THE SYNTHESIS AND REACTIONS OF SULPHUR ANALOGUES OF DEOXYVASICINONE

A THESIS SUBMITTED BY

Robert Norrie (B.Sc.)

in partial fulfilment of the requirements
of The Council for National Academic Awards
for the award of

DOCTOR OF PHILOSOPHY

Dundee Institute of Technology

JANUARY 1989

D E C L A R A T I O N

I hereby declare that the work presented in this thesis was carried out by me at Dundee Institute of Technology, Dundee, except where due acknowledgement is made, and has not been submitted by me for any other Degree.

Signed ..  ....

Date .....26.1.89.....

INDEX

ACKNOWLEDGEMENTS

The research described in this thesis was carried out in the organic chemistry research laboratory at Dundee Institute of Technology. Thanks are accorded to the Research Committee of the Institute for sanctioning this study and for the provision of the necessary research facilities and maintenance grant.

I would like to extend my sincere thanks to Dr A D Dunn for his guidance and encouragement during the course of this work. Thanks are also extended to Dr D H Bremner for his advice and suggestions during impromptu meetings.

Acknowledgement is made to the technicians of the Chemistry Section and the Library staff for their assistance and co-operation throughout the entirety of this project.

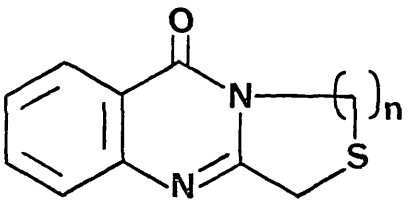
Finally I wish to thank Miss Diane Young for the typing of this manuscript.

The Synthesis and Reactions of Sulphur Analogues of Deoxyvasicinone

Robert Norrie B.Sc.

Abstract

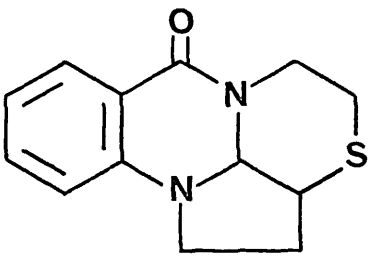
The synthesis of the thiazolo-, thiazino- and thiazepino-quinazolinones (A)-(C) was achieved, by the condensation of anthranilic acid with appropriate sulphur containing lactams, in the presence of phosphoryl chloride.
The quinazolinones (A) and (B) were shown to react (at the methylene group alpha to the carbon-nitrogen double bond) with a variety of electrophiles at elevated temperatures. Compound (C) was found to be inert to electrophiles under the same reaction conditions.
The ability of the heterocycles (A)-(C)to react with heterocumulenes, following deprotonation with sodium hydride in DMSO, was demonstrated. Reaction of the anion derived from (B) with alkylating agents, Michael acceptors and activated halopyridines afforded novel substituted derivatives.
The oxidation, Pummerer rearrangement and deacetylation of (A)-(C) was accomplished to yield analogues which were similar in structure to the biologically active compound vasicinone.
A series of C-ring substituted analogues of (A) were prepared and the sulphoxides derived from these compounds subjected to Pummerer rearrangement.
(A) and (B) were oxidatively ring opened on treatment with excess peracetic acid, whilst under similar reaction conditions (C) gave a sulphone.
Investigations into the reduction of substituted derivatives of (B) led to the novel tetracyclic compound (D).



(A) n = 1

(B) n = 2

(C) n = 3



(D)

FOREWORD

Bracketed Arabic numerals in the text refer to structures and the Arabic superscripts indicate references.

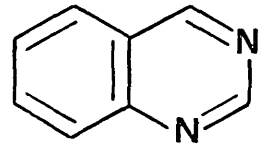
The following abbreviations have been used in the text.

m.p.	- melting point
m.m.p.	- mixed melting point
t.l.c.	- thin layer chromatography
p.l.c.	- preparative layer chromatography
Rf	- retention index for t.l.c.
ir	- infrared
p.m.r.	- proton magnetic resonance
J	- coupling constant
δ	- p.p.m.
Hz	- Hertz
DMSO	- dimethyl sulphoxide
DMF	- N,N-dimethylformamide
THF	- tetrahydrofuran
PTSA	- para-toluenesulphonic acid
Ac	- acyl
Ph	- phenyl
Et	- ethyl
Ts	- tosyl
Ar	- aryl

INTRODUCTION

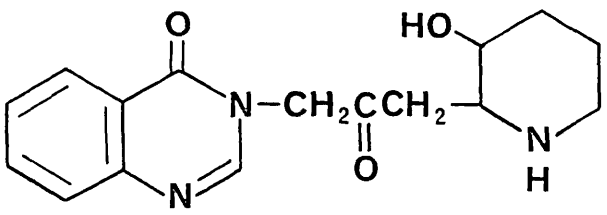
Introduction

The quinazoline ring system (1) is the building block for approximately eighty naturally occurring alkaloids which are widely distributed in nature (plants, microorganisms and animals). The diverse nature of biological activities exhibited by some of these alkaloids has prompted the synthesis and biological evaluation of many thousands of structurally similar substances and derivatives.



(1)

The isolation of febrifugine (2) from Dichro febrifuga (one of the ingredients of a traditional Chinese drug, effective in the treatment of malaria) provided a major stimulus for intensive study into the chemistry and pharmacology of quinazoline alkaloids. Compound (2) is apparently largely responsible for the antimalarial activity of this drug and was the first alkaloid, outside the cinchona group, found to possess marked antimalarial activity.



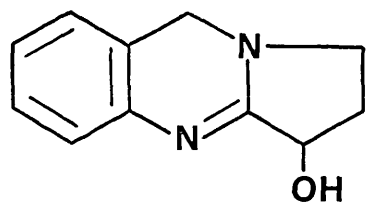
(2)

The pharmacological activity associated with the quinazoline moiety is well documented and two excellent review articles by Johne[1,2] are available, which report the wide range of biological activities shown by quinazolines, eg. as central nervous system depressants, anti-inflammatories, diuretics, antihypertensives and anti-allergics or as possessing anti-infectious, antimalarial, coccidiostatic or anthelmintic properties. In addition the use of quinazolines as fungicides[1,2], acaracide[3] and herbicides[4] has been reported. Currently, approximately fifty quinazoline derivatives are available for clinical use.

Deoxyvasicinone

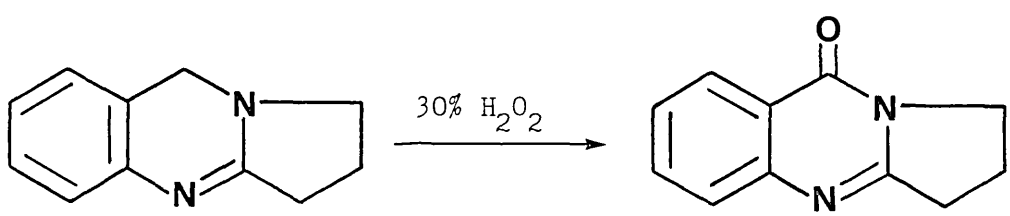
The first quinazoline alkaloid to be isolated, and indeed probably the best known, was vasicine (3). The compound (3) was first isolated by Hooper[5] in 1888 from the leaves of Adhatoda vasica Nees, a highly reputed Ayurvedic medicinal plant which has been used in Indian indigenous

medicine for over two thousand years. The crude medicines derived from Adhatoda vasica Nees are reputed to be especially effective in the treatment of respiratory ailments, particularly cough, bronchitis, asthma and tuberculosis.



(3)

In 1935, whilst investigating the structure of vasicine (3), Morris et al[6] obtained the previously unknown compound deoxyvasicinone (5) by the hydrogen peroxide oxidation of deoxyvasicine (4). (Scheme 1).

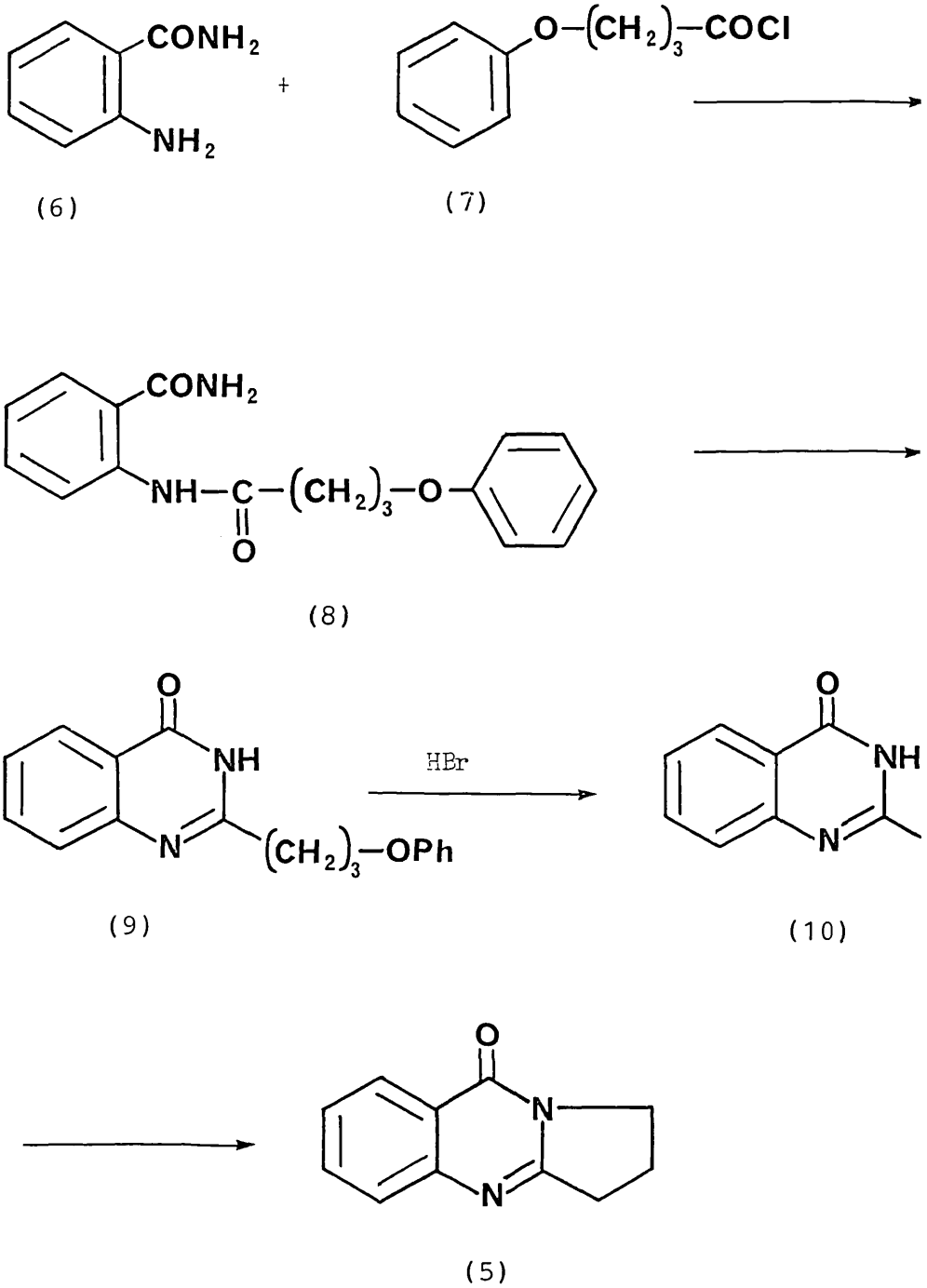


(4) (5)

Scheme 1

Deoxyvasicinone was assigned structure (5) following an unambiguous synthesis from anthranilamide (6) and 4-phenoxybutyryl chloride (7). Thermal cyclisation of the intermediate 2-(3-phenoxypropylamino)benzamide (8) gave 2-(3-phenoxypropyl)quinazolin-4-one (9). Reaction of the latter with hydrogen bromide led both

to bromination and removal of the phenoxy ether groupi to yield (10). Cyclisation of (10) in alkaline media gave deoxyvasicinone (5). (Scheme 2).

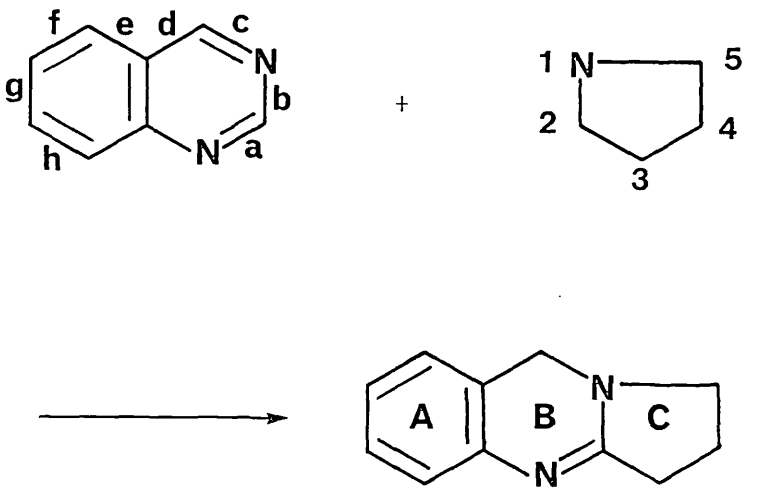


(6) (7) (8) (9) (10) (5)

Scheme 2

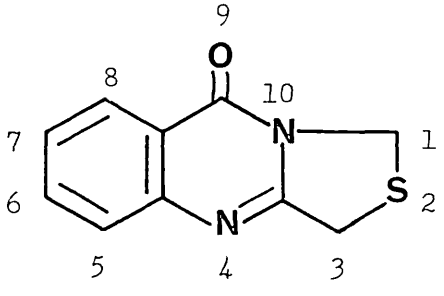
Nomenclature

Deoxyvasicinone (5) may be thought of as the product of fusion between a quinazoline nucleus and a pyrrolidine ring. The position of fusion is indicated by assigning letters to the peripheral bonds of the base component (ie quinazoline). Lettering is carried out alphabetically, starting from the 1,2 bond. The position of fusion is then indicated by inserting, in square brackets between the prefix (pyrrolo) and the base component, the locants of the position of attachment of the prefix component (in the order corresponding to the direction of lettering of the base component) followed by a hyphen and the letter corresponding to the bond of the base component.

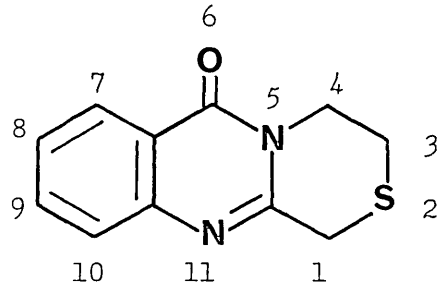


Thus according to this system deoxyvasicinone (5) will be 1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one. However, it should be noted that Chemical Abstracts use 2,3-dihydropyrrolo[2,1-b]quinazolin-9(1H)-one as the preferred name for deoxyvasicinone (5). Throughout this thesis the systematic nomenclature and numbering will be in accordance with that outlined in Chemical Abstracts.

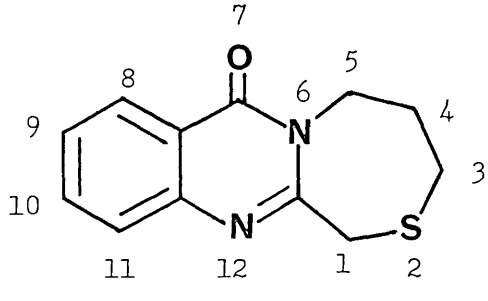
This thesis presents an account of the synthesis and reactions of analogues of thiazolo, thiazino and thiazepino quinazolines, in which the sulphur atom is incorporated β to the carbon-nitrogen double bond of the fused quinazoline. In all cases the sulphur containing ring is fused to the b face of the quinazoline moiety. Thus the systems examined are the thiazolo[4,3-b]-(11), thiazino[3,4-b]-(12) and thiazepino[3,4-b]-(13) quinazolinones. The numbering system used for these compounds is shown below.



(11)



(12)

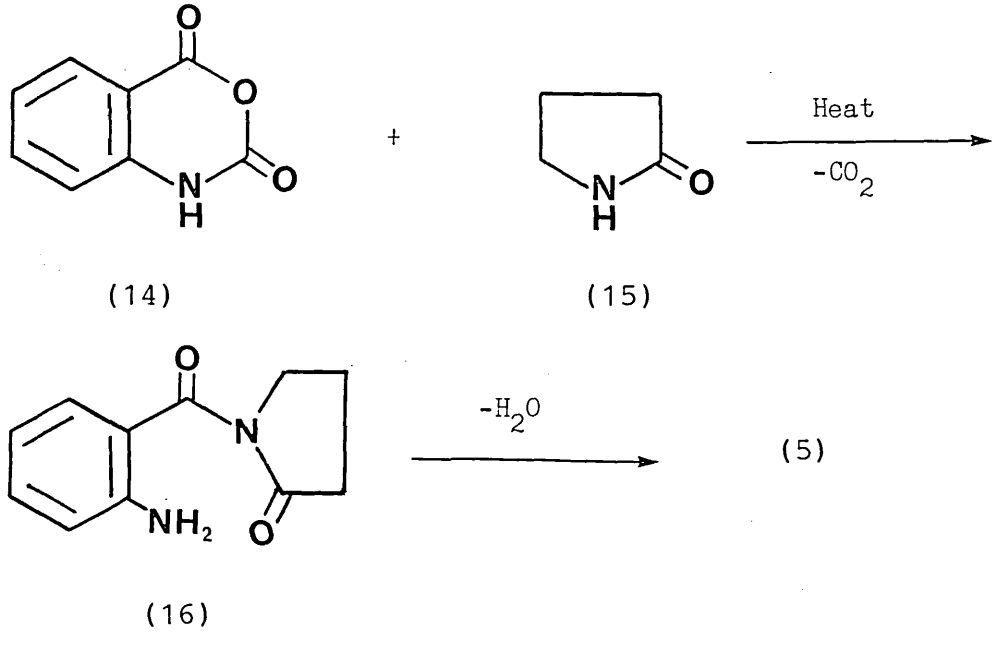


(13)

In order to put the results of this discussion into perspective it is pertinent to review relevant work carried out in the field of fused quinazoline chemistry.

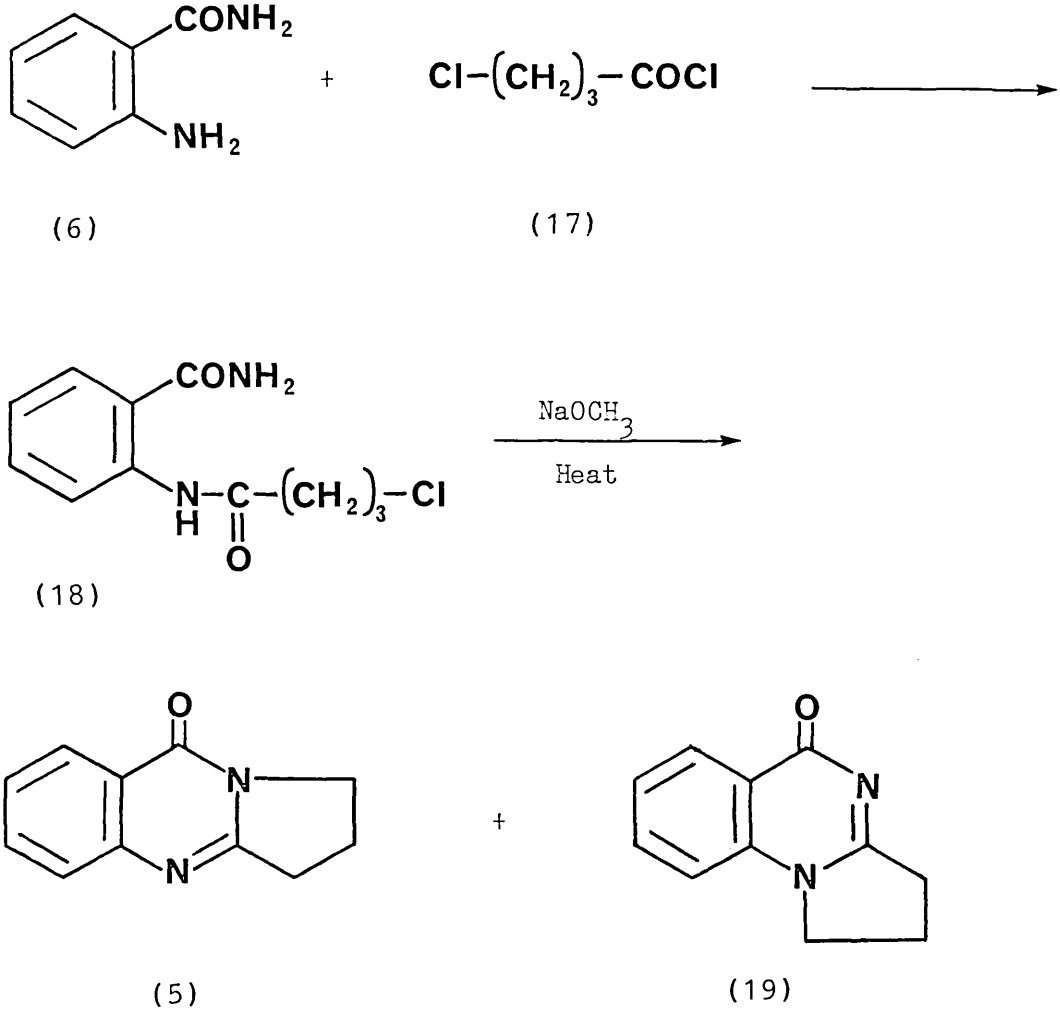
Synthesis of Deoxyvasicinone

Deoxyvasicinone (5) was found to be identical to the product 9-pegen-8-one, synthesised several months earlier than Morris[6], by Spath and Platzer[7]. Spath's synthesis involved the thermal fusion of 2-pyrrolidinone (15) with one equivalent of isatoic anhydride (14) at 120-130°C. The intermediate 1-(2-aminobenzoyl)pyrrolidinone (16) underwent ring closure with elimination of water to afford a compound which the authors named 9-pegen-8-one after Peganum harmala, the original floral source of alkaloids used by these workers. (Scheme 3).



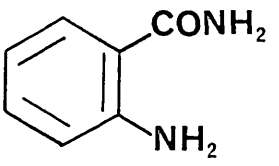
Scheme 3

As the interest in pyrroloquinazolinones, generated by the latent biological activity of these molecules, has grown, consequently so too has the number of synthetic routes to them. Landii Vittory and Gatta[8] developed a method for the preparation of both (5) and its [1,2-a] analogue (19), by the base catalysed thermal cyclisation of 2-(4-chlorobutyrylamino)benzamide (18), previously prepared from anthranilamide (6) and 4-chlorobutyryl chloride (17). (Scheme 4).



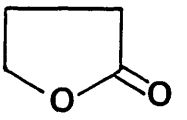
Scheme 4

Although this reaction is similar to that reported by Morris et al[6], in this case the nitrogen of the secondary amide can act as a nucleophile with subsequent formation of (19). The presence of the preformed quinazoline ring prohibits such a cyclisation in the Morris synthesis. The synthesis of both isomeric [1,2-a] and [2,1-b] pyrroloquinazolinones (5) and (19) and the analogous pyridoquinazolinones (22) and (23) have also been reported by Mohrle and Siedel[9], by heating anthranilamide (6) with γ-butyrolactone (20) or δ-valerolactone (21) at high temperature and pressure (in sealed tubes). (Scheme 5).

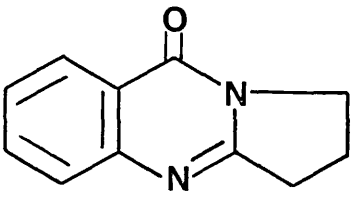


(6)

+

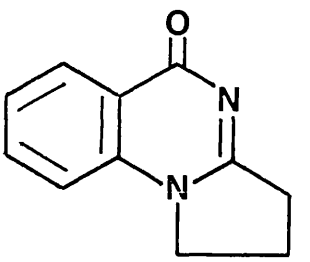


(20)

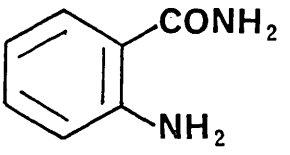


(5)

+

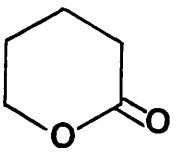


(19)

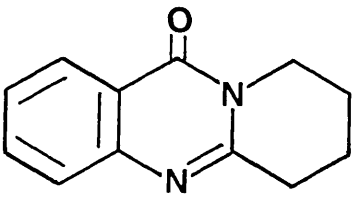


(6)

+

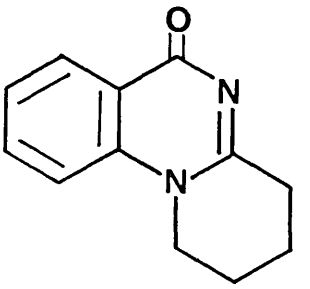


(21)



(22)

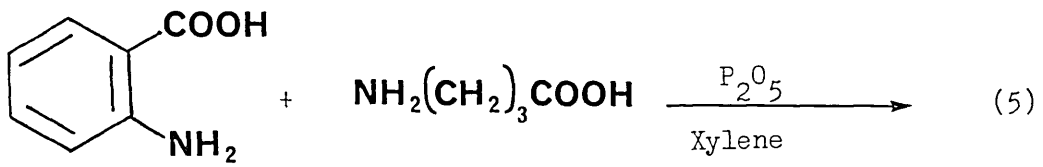
+



(23)

Scheme 5

Chatterjee and Ganguly[10] have demonstrated that deoxyvasicinone (5) can be prepared by the reaction of anthranilic acid (24) with 4-aminobutanoic acid (25) under dehydrating conditions, in an inert solvent. (Scheme 6).



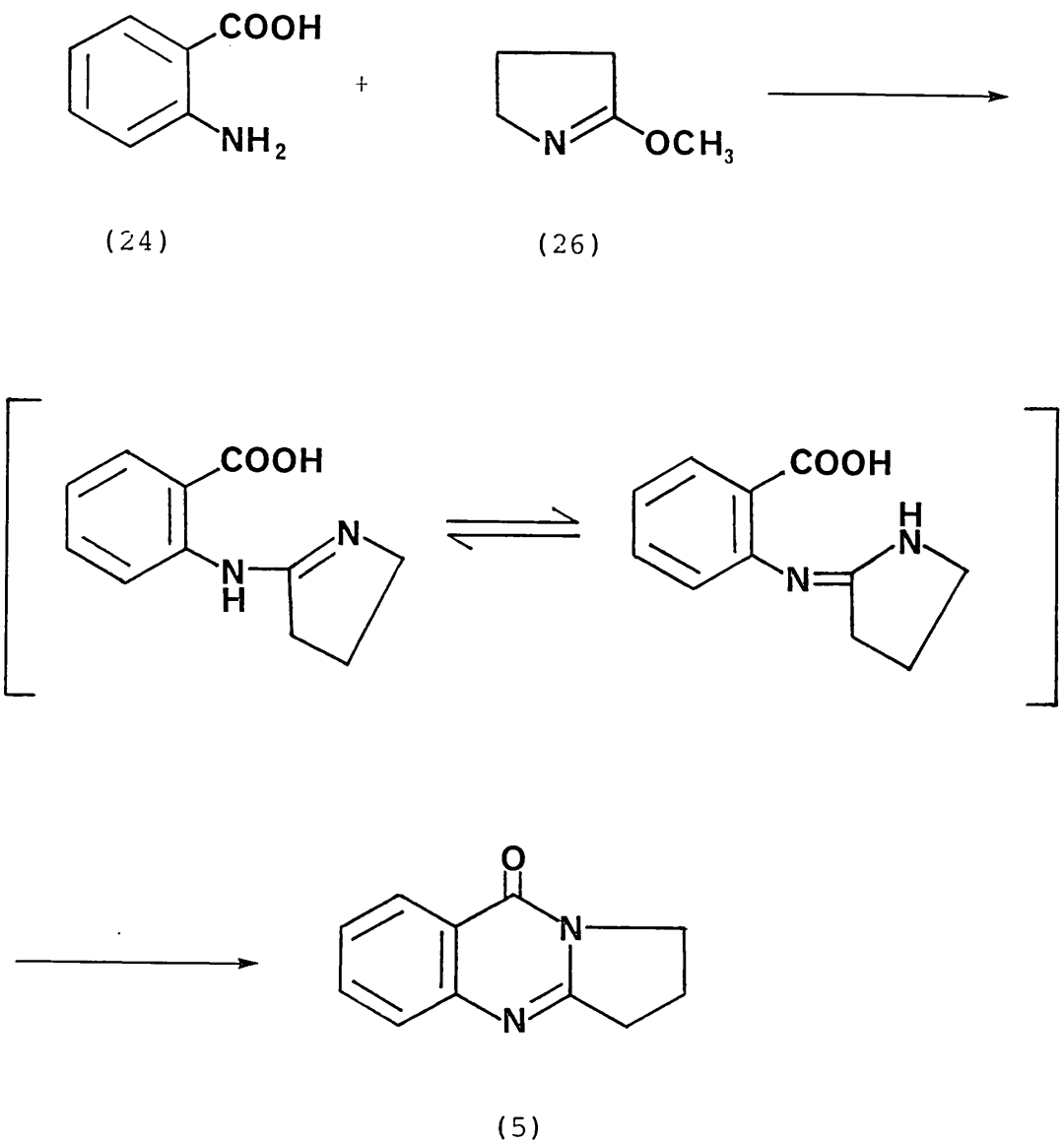
(24) (25)

Scheme 6

This method has been used by Johne et al[11] and Jain et al[12] in their respective investigations into nitrated A ring analogues of deoxyvasicinone (5). Although the aforementioned synthetic routes are effective and allow the preparation of pyrroloquinazolinones in reasonable yield, they are unsatisfactory in that they are usually capricious, circuitous or time consuming and often result in the formation of isomeric compounds.

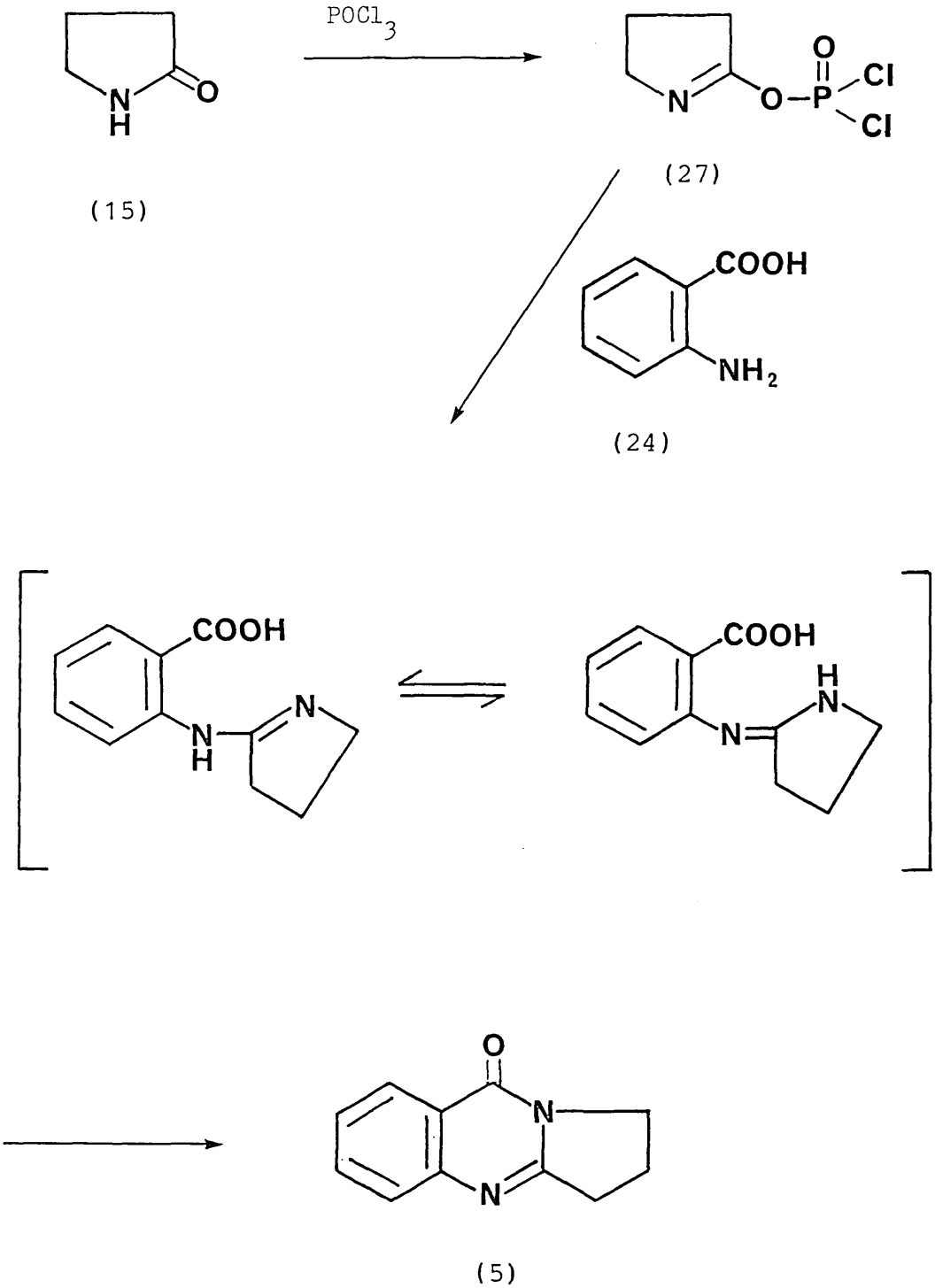
A number of new preparatory routes, which circumvent these problems have been developed, which employ the condensation reaction between anthranilic acids and cyclic amides or their O-alkyl ethers. Peterson and Tietze[13] prepared pyrrolo-, pyrido- and azepino[2,1-b]quinazolinones, in high yield using mild conditions, by the reaction of an anthranilic acid with a cyclic lactim ether. Generally the

reaction proceeds by mixing the cyclic lactim ether and the acid in a suitable solvent, or in some cases neat. Ring closure is usually spontaneous, although occasionally, heating is sometimes necessary. The reaction is thought to be a two stage process, the initial step being formation of a reactive cyclic amidine. Cyclisation of this amidine, with elimination of a mole of water, following a tautomeric shift leads to tricycles. The reaction is illustrated by the synthesis of (5) from 2-methoxy-1-pyrroline (26) and anthranilic acid (24). (Scheme 7).



Scheme 7

The intermediate amidine, formed by nucleophilic displacement of the methoxy ether grouping by the amino group of the anthranilic acid, spontaneously rearranges to its tautomer, the existence of which is not unreasonable since enamine-imine tautomerism is well documented. Cyclisation then takes place via reaction of the sp^3 hybridised nitrogen of the pyrrolidine ring with the carboxyl grouping. Shakhidoyatov et al[14] have described the preparation of pyrrolo-, pyrido- and azepino[2,1-b] quinazolinones by the reaction of lactams with anthranilic acid (24) in the presence of a dehydrating agent such as phosphoryl chloride, thionyl chloride or a mixture of phosphorus trichloride and phosphorus pentachloride. For example, the reaction between 2-pyrrolidinone (15) and anthranilic acid (24) in phosphoryl chloride yields deoxyvasicinone (5). The reaction is thought to proceed by reaction of the lactam (15) with phosphoryl chloride to give the cyclic imine (27). This was substantiated following treatment of 2-pyrrolidinone (15) with phosphoryl chloride at room temperature. An exothermic reaction is observed with vigorous evolution of hydrogen chloride. The reaction of this Vilsmeier type imine (27) and anthranilic acid (24) yields a cyclic amidine which cyclises, following rearrangement, to give deoxyvasicinone (5). (Scheme 8).



Scheme 8

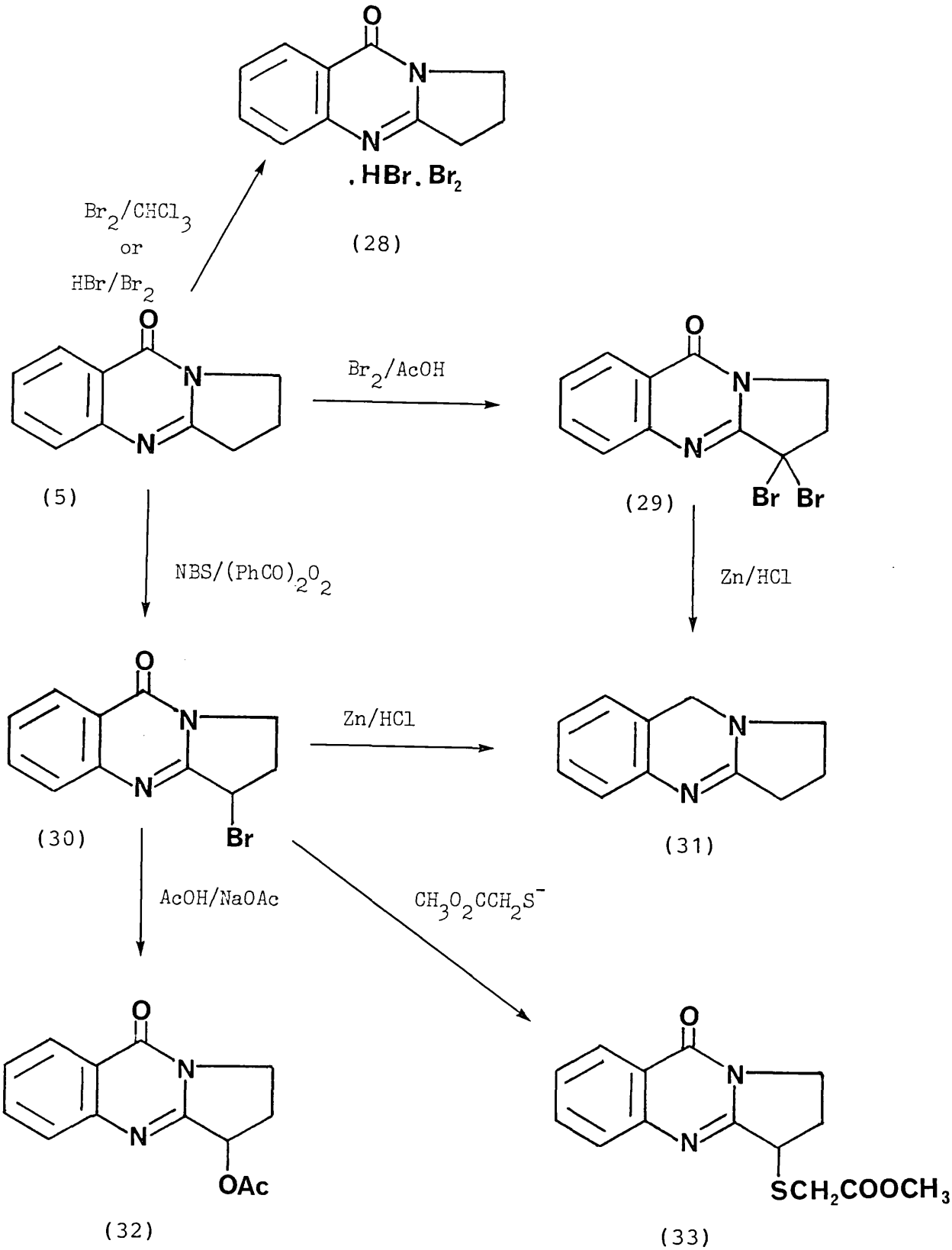
This synthetic route has been used by Shakhidoyatov to prepare a range of pyrrolo-, pyrido- and azepino[2,1-b] quinazolinones. The effect of introducing substituents into the A and C rings via substituted anthranilic acids and substituted lactams respectively was also investigated. The reactivity of various lactams was shown to decrease with increasing ring size and with the introduction of substituents (chloride and phenyl), whilst the introduction of substituents (nitro, amino and halo) into the aromatic nucleus had little effect on the subsequent yield of product.

The methods derived from the techniques of Shakhidoyatov and Peterson and Tietze have obvious advantages over the earlier routes to fused quinazolinones. Single products result in both cases and they are both relatively simple one step reactions.

Reactions of Deoxyvasicinone

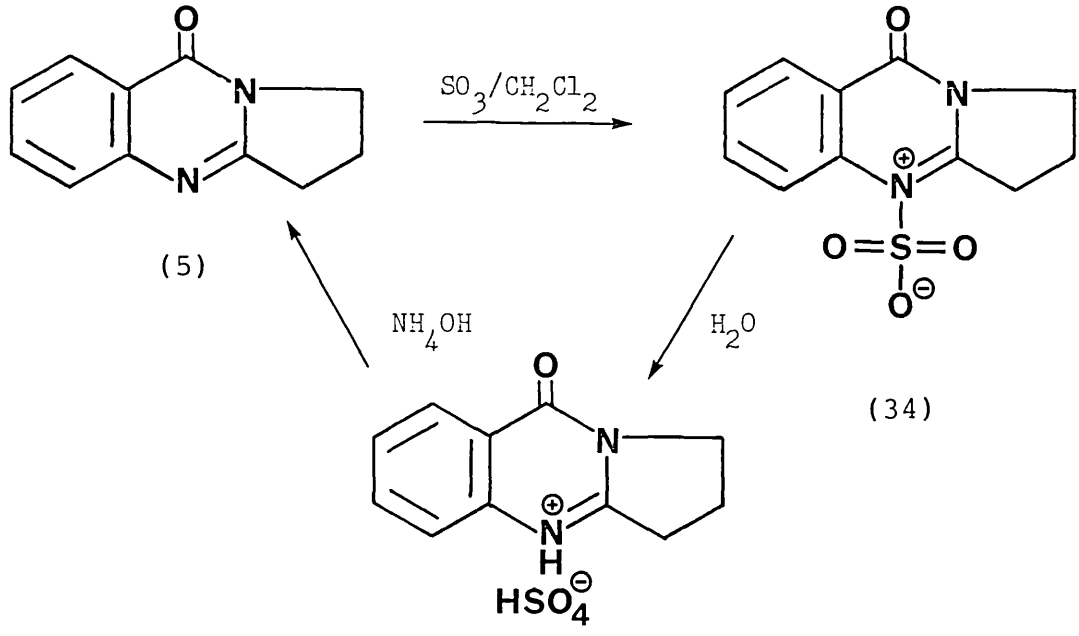
The reaction of deoxyvasicinone (5) and a number of its higher analogues with electrophilic reagents has been reported as following three main reaction pathways. Reaction may occur at the aromatic ring by electrophilic aromatic substitution, at the active methylene group (C-3) or at the sp^2 hybridised nitrogen atom.

The bromination of pyrrolo-, pyrido- and azepino[2,1-b] quinazolinones was investigated by Oripov et al[15,16], who found that the reaction product was dependent upon the brominating agent and the solvent system employed. (Scheme 9). Bromination of (5) in various solvents (chloroform, glacial acetic acid, concentrated sulphuric acid and 80% methanol) afforded the perbromide (28) when the reaction was carried out in the cold, with or without catalysis. The perbromide (28) was also obtained from the reaction of (5) with hydrogen bromide and bromine. Bromination of (5), by heating the latter with bromine in 75% acetic acid, gave only the 3,3-dibromo derivative (29). The 3-monobromo derivative (30) is accessible by using the more selective N-bromosuccinimide, in the presence of benzoyl peroxide as initiator, in carbon tetrachloride . Treatment of the monobromo compound (30) with acetic acid and sodium acetate gave acetylvasicinone (32), whilst treatment with thioglycolate anion afforded (33). Interestingly no aromatic bromination occurred despite the use of ferric chloride or other halogen carriers in these bromination reactions. Reduction of (29) or (30) resulted in the elimination of bromine to give deoxyvasicine (4).


.HBr.Br2
(28)
Br2/CHCl3
or
HBr/Br2
Br2/AcOH
(5)
(29)
Br Br
NBS/(PhCO)2O2
Zn/HCl
Zn/HCl
(30)
Br
(31)
AcOH/NaOAc
CH3O2CCH2S−
OAc
(32)
SCH2COOCH3
(33)

Scheme 9

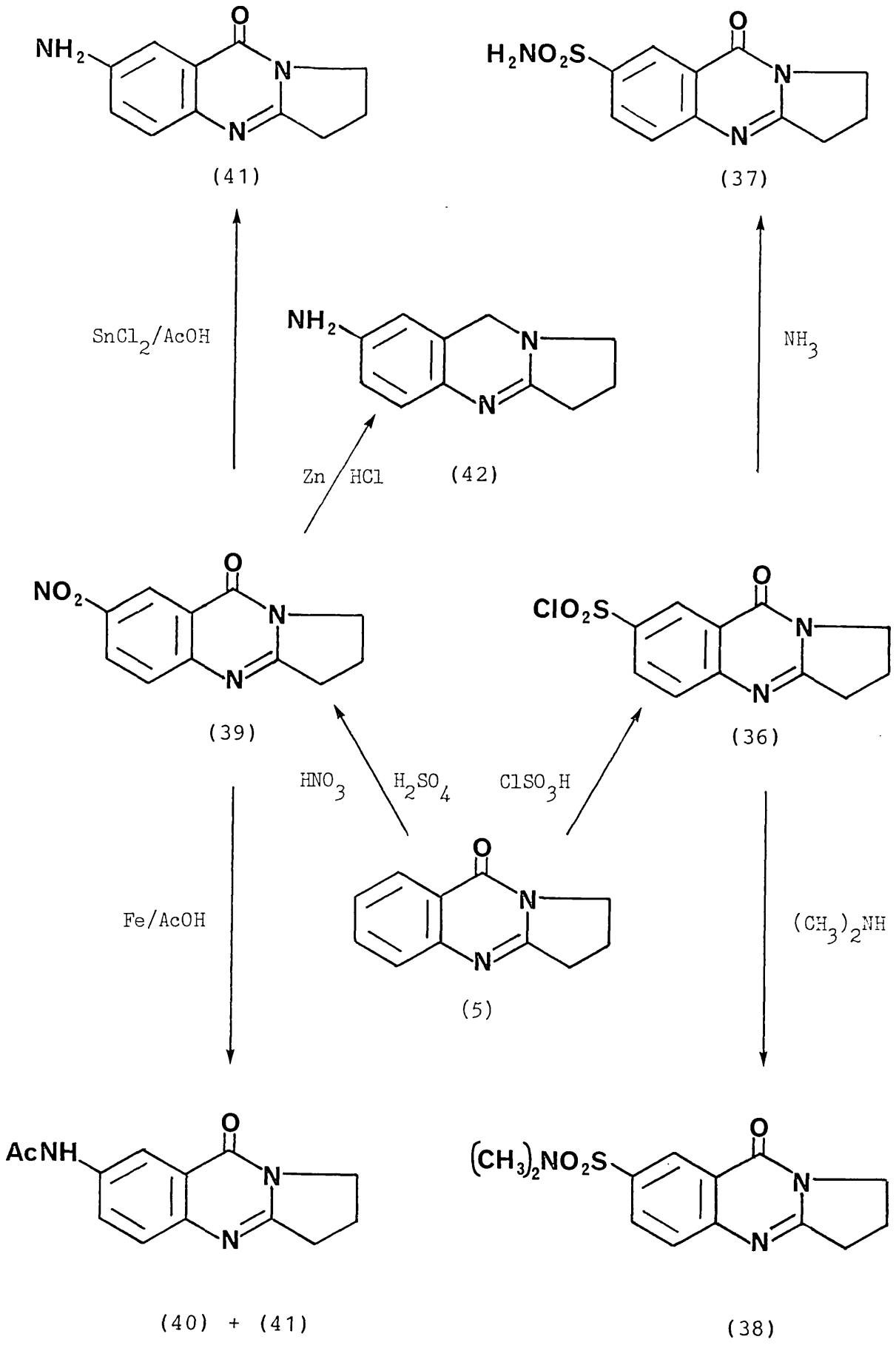
The sulphonation[16] of deoxyvasicinone (5) can be effected using sulphur trioxide in dichloromethane. The complex (34) formed from attack at the 4-position may be easily hydrolysed to give the hydrogen sulphate salt (35). Treatment of (35) with ammonium hydroxide regenerates (5). (Scheme 10).



Scheme 10

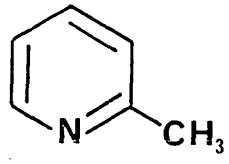
Chlorosulphonation[16] of deoxyvasicinone (5), in contrast to bromination and sulphonation, yields a product of electrophilic aromatic substitution. The 7-chlorosulphonyl derivative (36) thus obtained may be reacted with ammonia or dimethylamine to yield the 7-sulphonamido- and 7-(N,N-dimethylsulphonamido)- derivatives (37) and (38).

Nitration[16] of deoxyvasicinone (5) with a mixture of nitric and sulphuric acids gives the 7-nitro-derivative (39). Reduction of the nitro group in (39) with iron in glacial acetic acid affords both the 7-amino- and 7-acetylamino deoxyvasicinones (40) and (41) in a total yield of 56%. Reduction of (39) in the presence of stannous chloride afforded only (41) in 90% yield. More drastic reduction of (39) using zinc and hydrochloric acid afforded 7-aminodeoxyvasicine (42) in excellent yield. (Scheme 11).

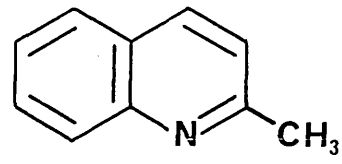

NH2
(41)
H2NO2S
(37)
SnCl2/AcOH
NH3
NH2
Zn HCl
(42)
NO2
(39)
ClO2S
(36)
HNO3
H2SO4
ClSO3H
Fe/AcOH
(CH3)2NH
(5)
AcNH
(40) + (41)
(CH3)2NO2S
(38)

Scheme 11

Deoxyvasicinone (5) undergoes a number of interesting chemical transformations at the C-3 methylene group. The protons at this position bear a strong resemblance to the protons of the methyl group in 2-picoline (43) and quinaldine (44).

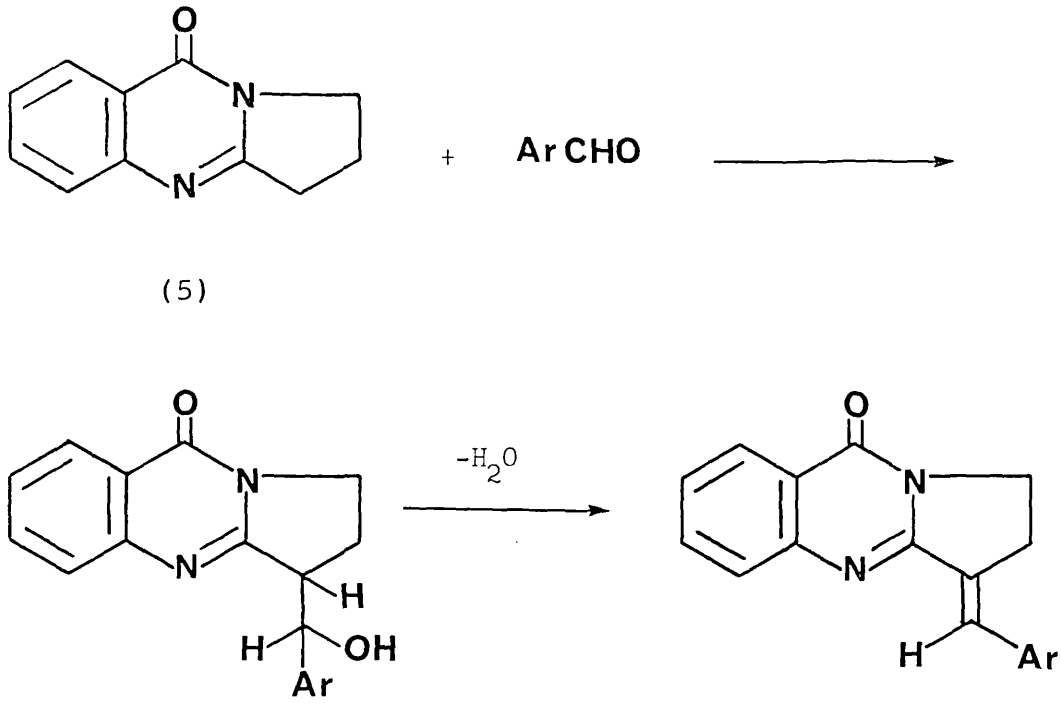


(43)



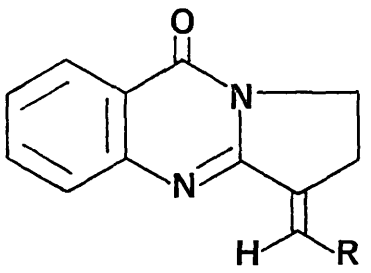
(44)

However, the fact that deoxyvasicinone (5) condenses with aromatic aldehydes with no catalysis indicates they are much more reactive. Despite this reactivity, and the fact that a similar reactive methylene group has been observed in the [1,2-a] analogue (19) by Taylor and Shvo[17], little use has been made of this reactivity in the preparation of novel alkaloids. 3-Arylidene derivatives have been prepared by several groups,[6,12,18,19,20,21] by the condensation of deoxyvasicinone (5) and aromatic aldehydes. When 3- or 4-nitrobenzaldehyde is used the intermediate alkanol may be isolated. (Scheme 12).



Scheme 12

Although heterocyclic aldehydes such as furfural (furan-2-aldehyde) also undergo reaction, aliphatic and unsaturated aldehydes were shown to be unreactive at atmospheric pressure[20]. Jain and Sharma[19] have recently reported the formation of seven derivatives (45) - (51) from the reaction of deoxyvasicinone (5) with aliphatic and unsaturated aldehydes at elevated pressures. However, no spectral evidence was provided in support of these claims.



(45) R = CH=CH-Ph

(46) R = CH_3

(47) R = CH_2CH_3

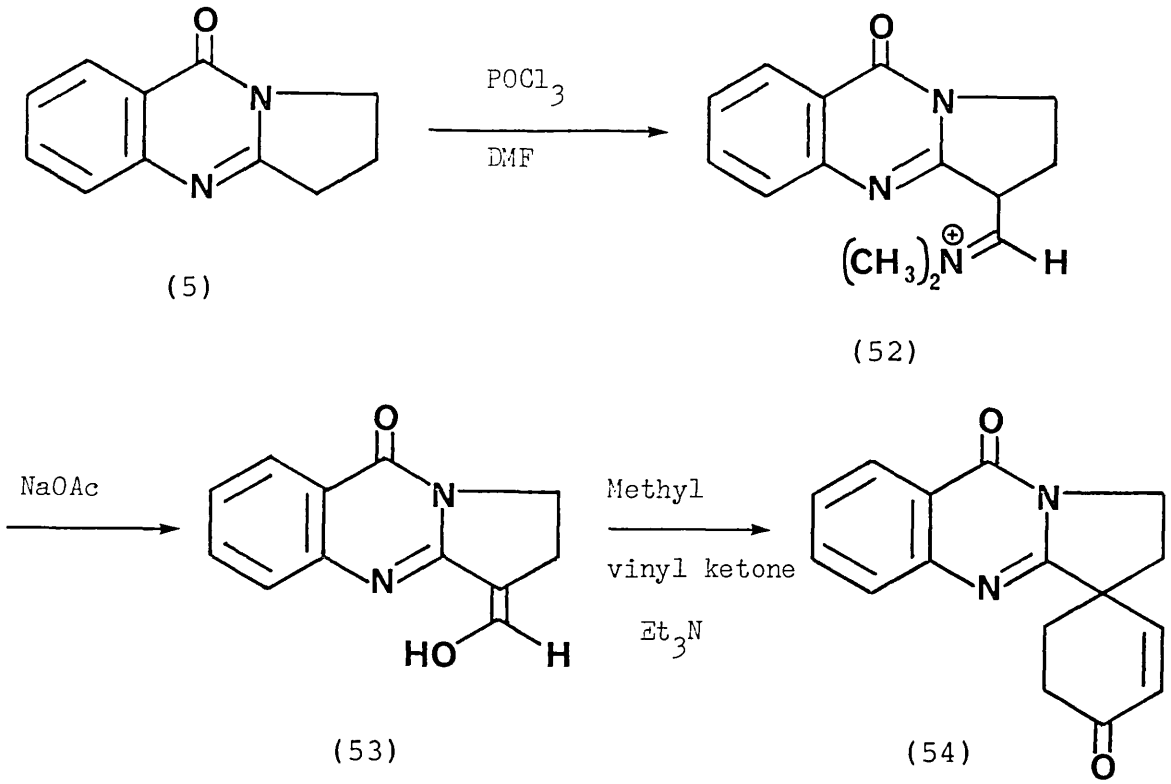
(48) R = $(CH_2)_2CH_3$

(49) R = $(CH_2)_3CH_3$

(50) R = $CH_2CH(CH_3)_2$

(51) R = CH=CH-CH_3

Vilsmeier-Haack formylation[22] of (5) yields the intermediate (52) which can be converted to the hydroxymethylene derivative (53) by treatment with an aqueous solution of sodium acetate. The hydroxymethylene compound (53) can undergo a Robinson type annulation with methyl vinyl ketone in the presence of triethylamine to give the spiroenone (54)[23]. (Scheme 13).



(5)

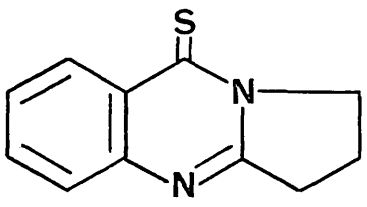
(52)

(53)

(54)

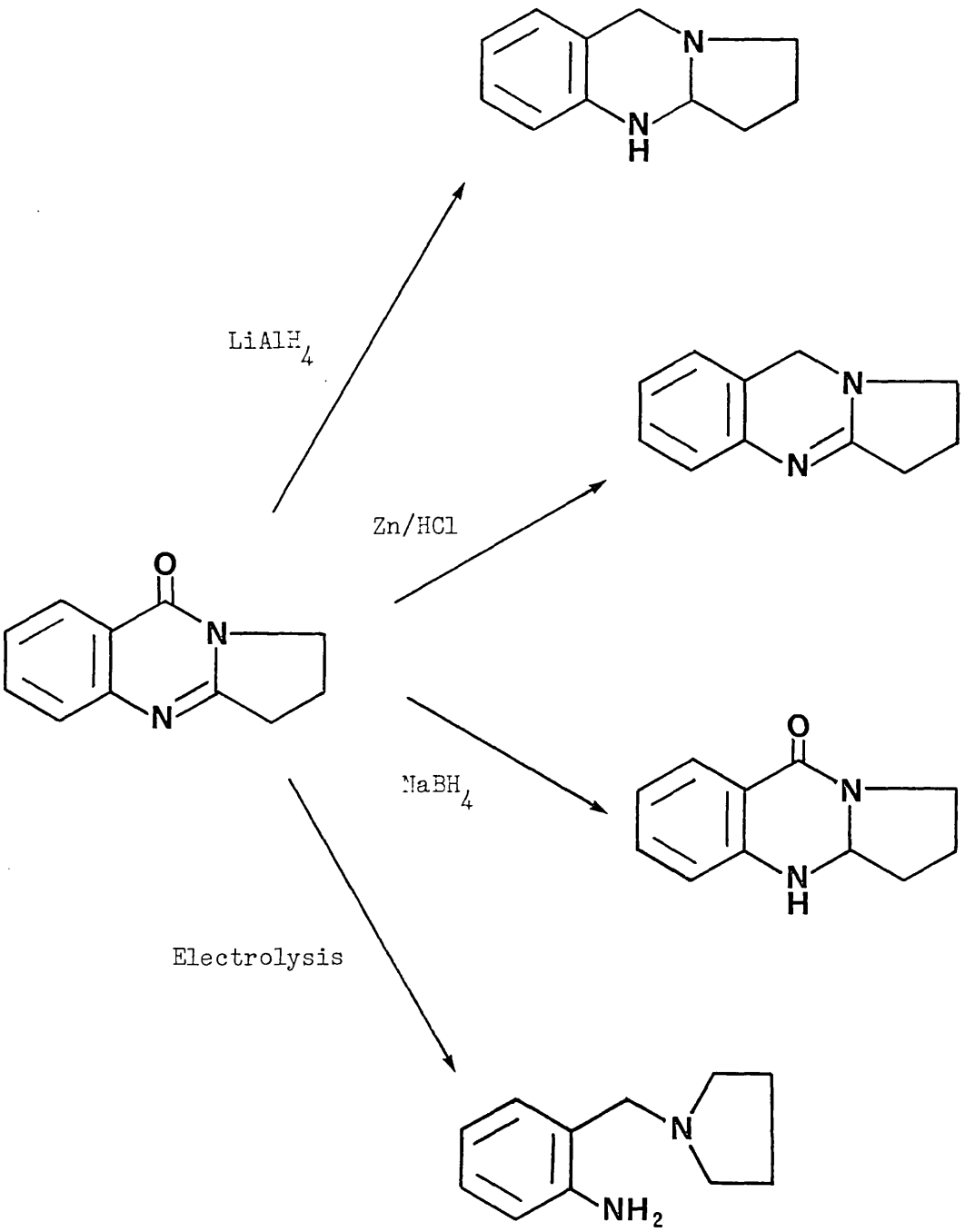
Scheme 13

Treatment of deoxyvasicinone (5) with phosphorus pentasulphide yields the 9-thio analogue (55) which can be reduced in the presence of zinc and hydrochloric acid to deoxyvasicine (4)[24].



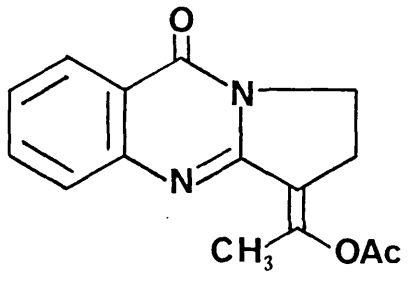
(55)

A number of techniques have been used to reduce deoxyvasicinone (5). Reduction of the carbonyl group can be effected by dissolving metal reduction[25,26], whilst selective reduction of the carbon-nitrogen double bond has been achieved using sodium borohydride [8,27]. Simultaneous reduction of both functional groups occurs with lithium aluminium hydride[8]. Electrolytic reduction leads to rupture of the quinazoline ring and the formation of N-(2-aminobenzyl)pyrrolidine[28]. (Scheme 14). Although C and N acylation of the [1,2-a] analogue (19) by hot acetic anhydride in pyridine has been reported[17], this technique proved ineffectual when applied to deoxyvasicinone (5). However, when deoxyvasicinone (5), or its hydrochloride, was heated at reflux for prolonged periods with

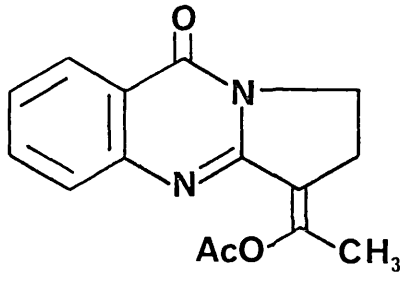


Scheme 14

excess acetic anhydride, two isomeric enol acetates (56) and (57) resulted[29]. The same enol acetates were also obtained, in low yield, when deoxyvasicinone (5) was heated with acetyl chloride.

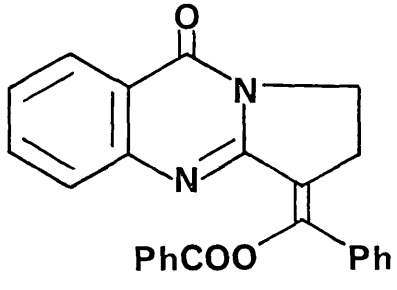


(56)

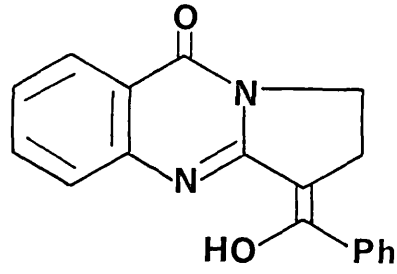


(57)

When deoxyvasicinone (5) was heated with benzoic anhydride, condensation occurred at 230°C to give two compounds of almost identical Rf[30], which were eventually separated by repeated fractional crystallisation. The major product was identified as the enol benzoate (58), with the Z stereochemistry being assumed for steric reasons. The minor product was identified as the Z-hydroxybenzylidene derivative (59) by an X-ray crystallographic study[31], which also indicated the presence of a weak hydrogen bond between the hydroxyl hydrogen atom and the sp^2 nitrogen atom.

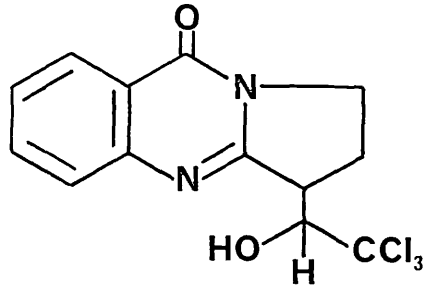


(58)



(59)

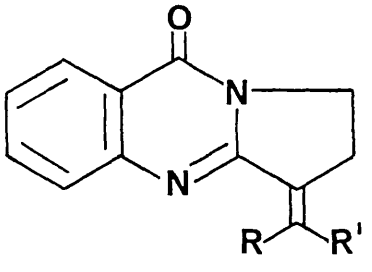
The condensation between 2-picoline (43) and chloral hydrate has been known for over one hundred years[32]. More recently, Taylor and Shvo[17] have shown that [1,2-a]quinazolinones also undergo condensation with this reagent. When deoxyvasicinone (5) was heated gently with excess chloral hydrate the trichlorohydroxyethyl derivative (60) was isolated[29].



(60)

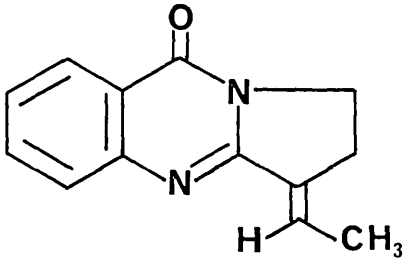
This result prompted Dunn and Kinnear[29] to investigate the reaction of deoxyvasicinone (5) with other reagents possessing halogen atoms α to a carbonyl group. Reaction of (5) with chloroacetyl chloride or dichloroacetyl chloride afforded the chloroethylidene derivatives (61) and (62) respectively, whilst reaction of (5) with

trichloroacetyl chloride gave the enol (63).



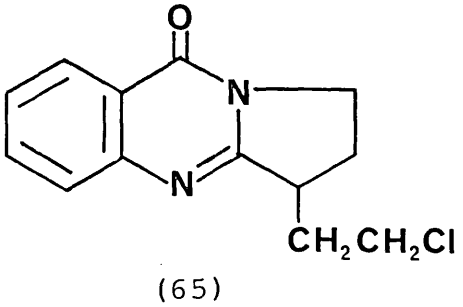
	R	R'
(60)	$ClCH_2$	Cl
(61)	Cl_2CH	Cl
(62)	OH	CCl_3

The reduction of (61) with sodium borohydride in ethanol gave two products, the more polar of which was identified as the ethylidene derivative (64).

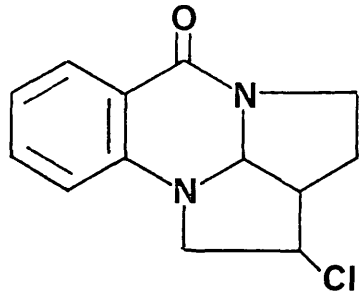


(64)

The less polar component was shown by elemental analysis and mass spectrometry to have the formula $C_{13}H_{13}ClN_2O$ and, although its actual structure has not been ascertained, the authors have proposed (65) or (66) as the most likely structure.

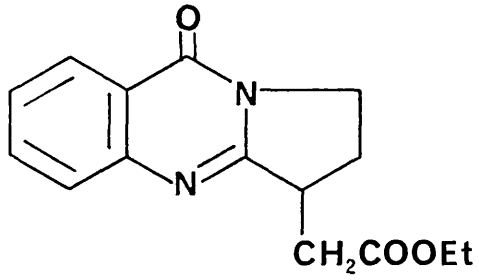


(65)

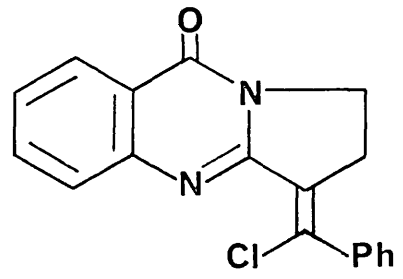


(66)

However, structure (65) would appear to be more likely since the position of the carbonyl in the infrared spectrum (1680 cm^{-1}) is not consistent with that of a reduced quinazoline (1640 cm^{-1}). Deoxyvasicinone (5) also underwent condensation with ethyl chloroacetate or ethyl bromoacetate to give the ethoxycarbonylmethyl derivative (67) and with benzoyl chloride to give the chlorobenzylidene compound (68).

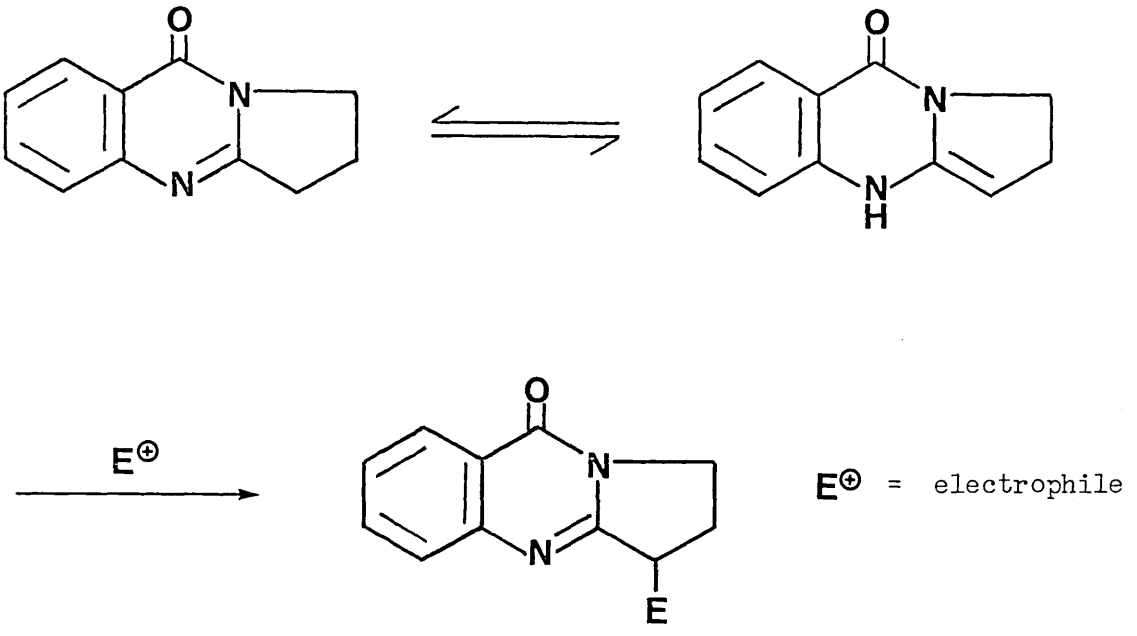


(67)



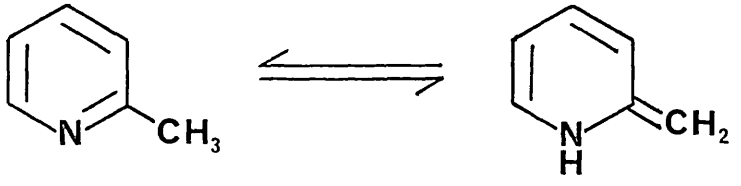
(68)

Two possible mechanisms to account for this reactivity at C-3 have been postulated. The first involves the protopic enamine tautomer of the original fused quinazolinone, the formation of which would lead to classical enamine reactions. (Scheme 15).



Scheme 15

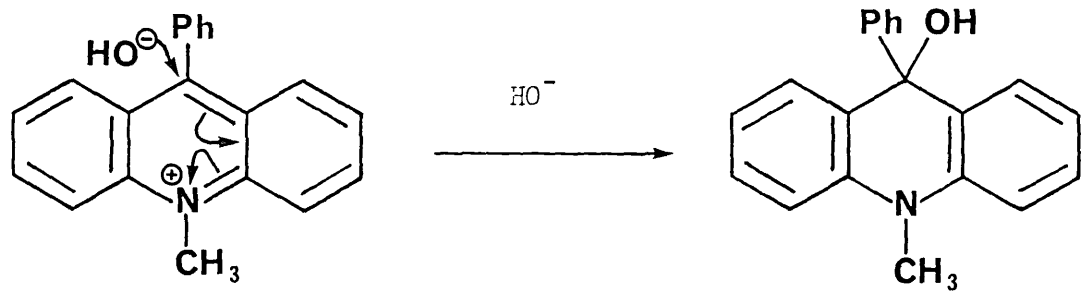
This is similar to the mechanism proposed by Tschitschibabin[33] to account for the reactivity of the methyl group in 2-picoline (43). (Scheme 16).



(43)

Scheme 16

The second proposal is that the reactivity at C-3 of deoxyvasicinone (5) may be due to the formation of a pseudo-base. Hantzsch[34] was the first to recognise a form of tautomeric change in the reversible conversion between ionised quaternary ammonium hydroxides having double-bonded nitrogen and the isomeric non-ionic carbinols. The latter he termed pseudo-bases. One of his original examples was that of 5-phenyl-10-methylacridinium hydroxide and its salts. The salts with strong acids, such as hydrochloric acid, are typical quaternary ammonium salts. However, on treatment with a sufficiently nucleophilic anion, such as hydroxide, the covalent molecule (69) is predominantly produced. (Scheme 17).

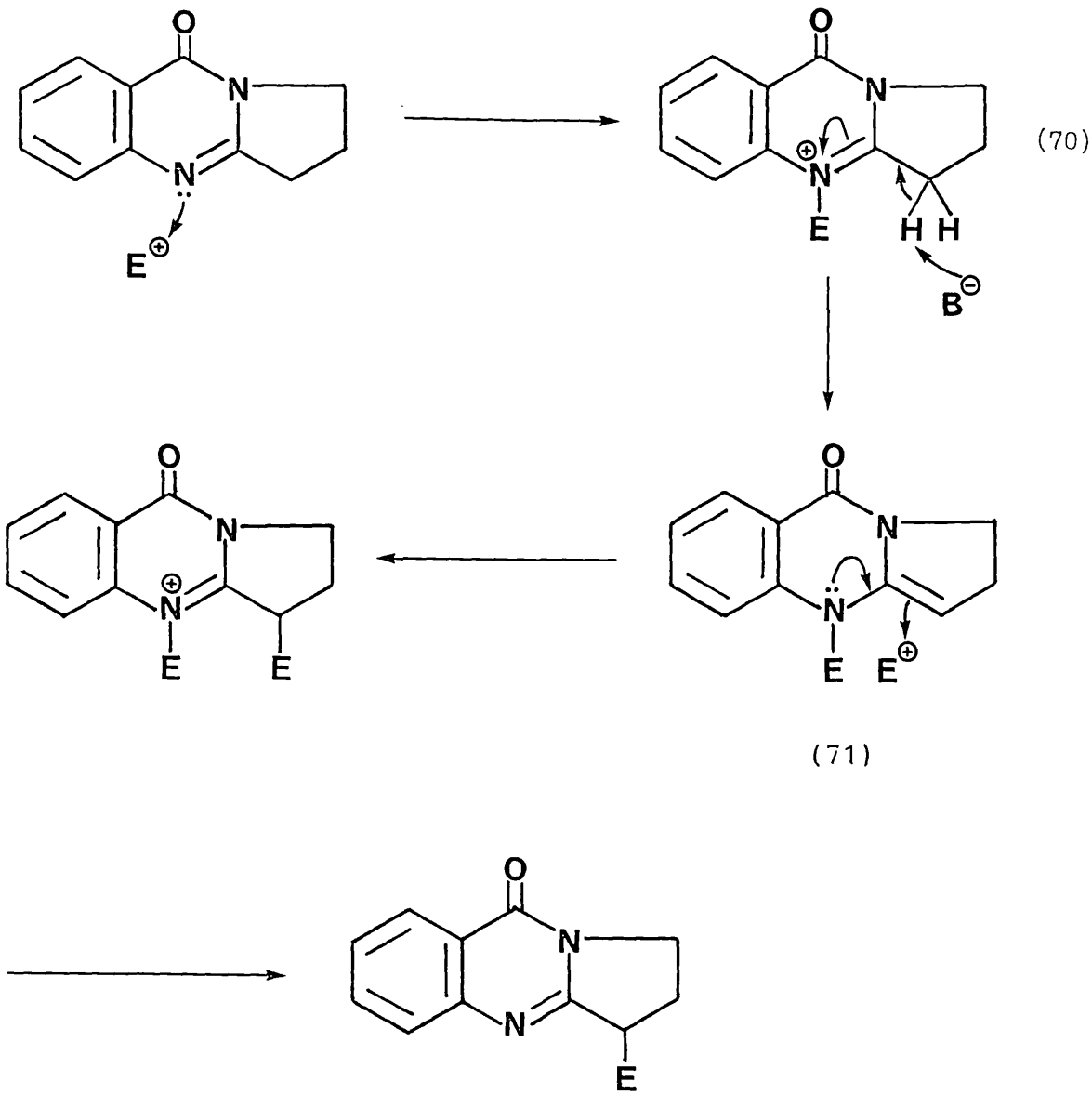


(69)

Scheme 17

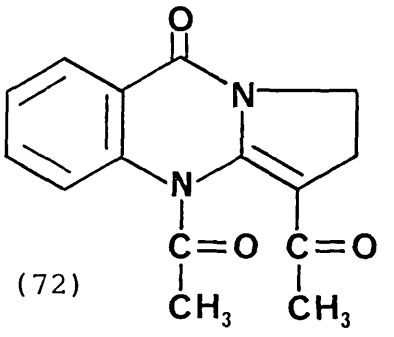
The formation and subsequent reaction of such a pseudo-base of deoxyvasicinone (5) may be reasoned as follows. Nucleophilic attack by the lone pair of the sp^2 nitrogen atom results in initial formation of a quaternary ammonium salt (70).

Electron migration and attack by a basic anion would eventually lead to the formation of the C-alkylated product via the pseudo-base (71).



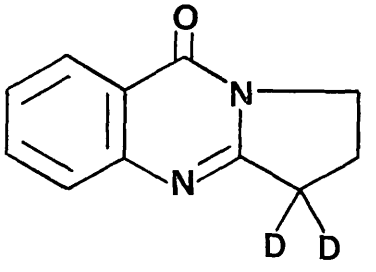
Scheme 18

The latent enamine type reaction mechanism is thought to be the more feasible, since no carbamate derivatives of the type (72) have ever been isolated and although hydrolytic cleavage at the carbon-nitrogen bond should not be discounted, the absence of any N-alkylated/acylated products would seem to indicate that the pseudo-base mechanism is very unlikely.



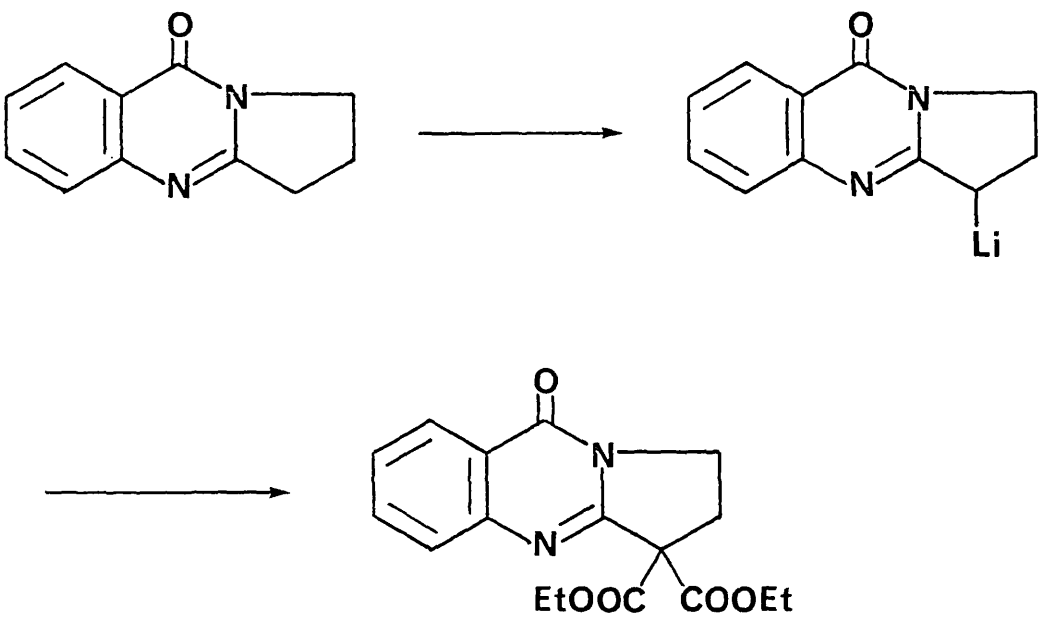
(72)

Furthermore, the presence of the enamine tautomer of (5) at high temperature has been demonstrated in a deuterium exchange study[35]. When deoxyvasicinone (5) was heated at 150°C for fifteen hours with excess deuterium oxide (sealed tube), complete exchange of the C-3 hydrogen atoms occurred and the 3,3-dideuterio derivative (73) was recovered in 80% yield.



(73)

Although early experiments had shown that the deprotonation of deoxyvasicinone (5) in a variety of solvent/base mixtures had failed, it was later found that (5) could be metallated at -20°C using lithium diisopropylamide in dry THF[30]. Reaction of the intermediate organometallic species with ethyl chloroformate gave the diester (74) in 28% yield.

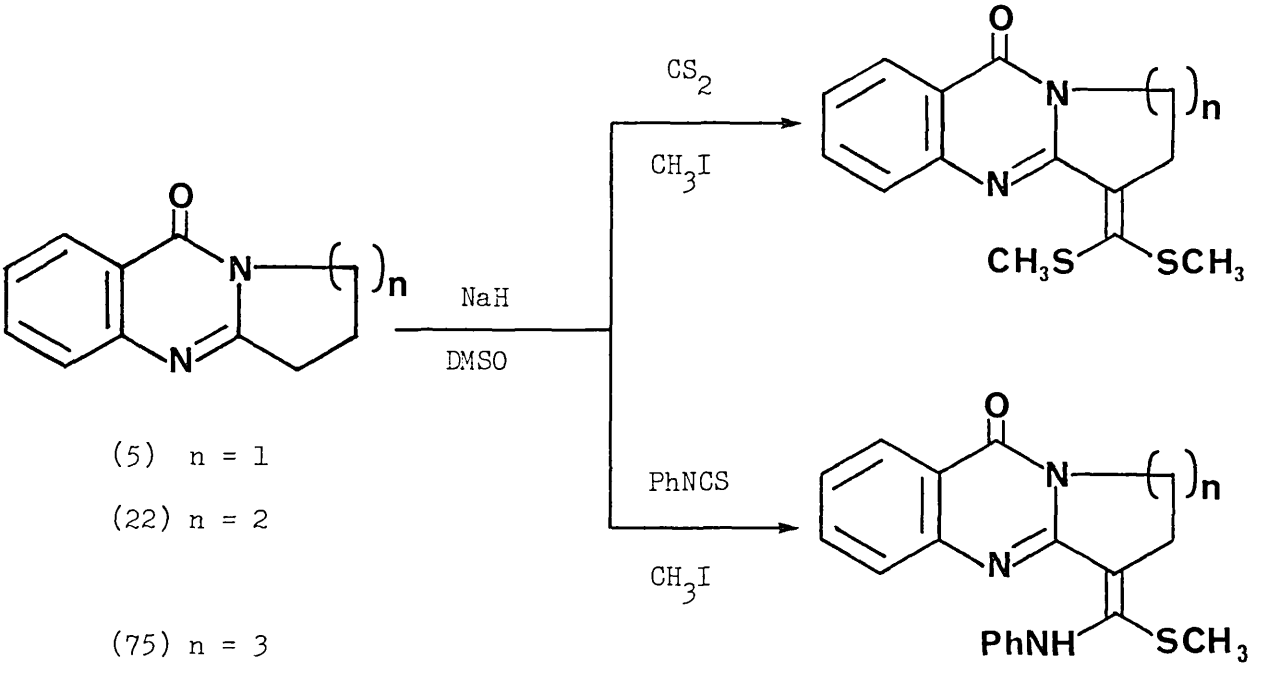


(74)

The formation of the diester (74), in low yield, is thought to be as a result of lithiation of an intermediate monoester by a mole equivalent of original lithiated deoxyvasicinone (5). Such an exchange reaction would not be unexpected since the remaining proton at C-3 in the intermediate monoester would be rendered much more acidic due to the electron withdrawing effect of the ester group. Treatment of lithiated deoxyvasicinone with other electrophiles gave

no new products.

More recently[36], deoxyvasicinone (5) and the pyrido-quinazolinone (22) has been deprotonated using sodium hydride in dimethyl sulphoxide and the resulting anions trapped with carbon disulphide or phenyl isothiocyanate. Methylation with iodomethane gave ketene S,S and S,N acetals respectively. The azepino quinazolinone (75) was found to be unreactive under the same conditions. (Scheme 19).



(5) n = 1

(22) n = 2

(75) n = 3

n = 1 or 2 only

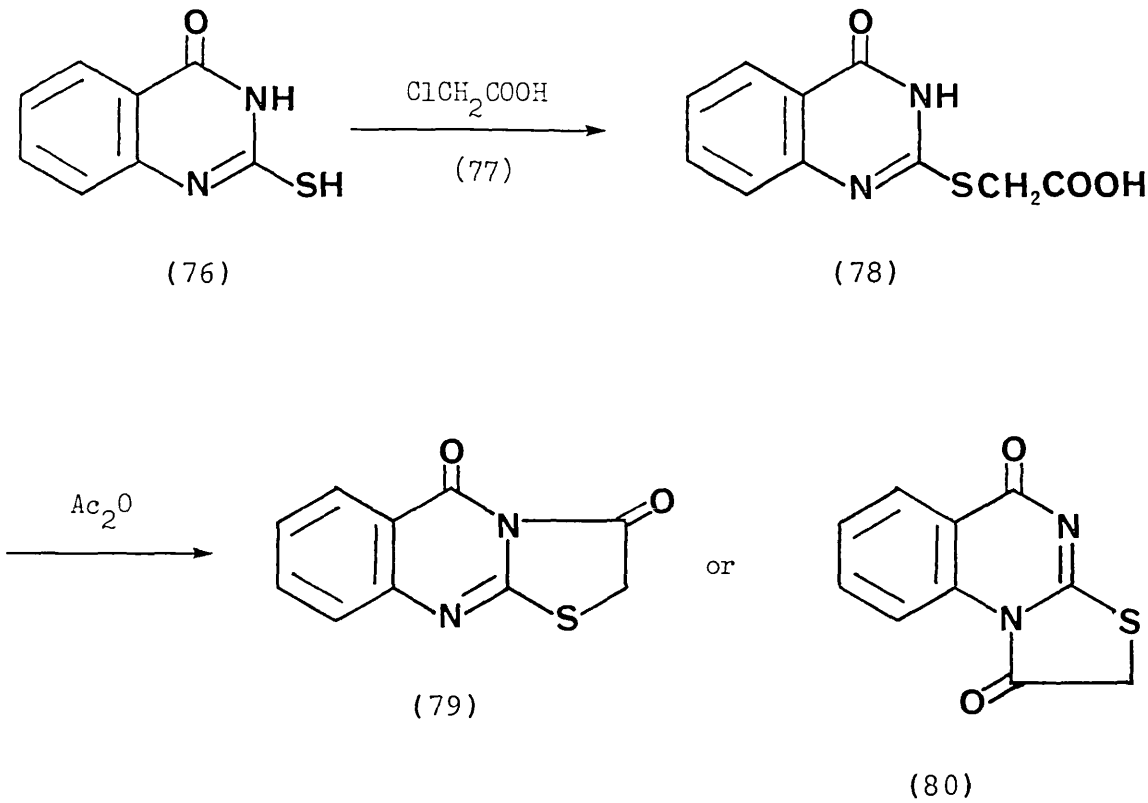
Scheme 19

The ketene S,N-acetals, which appear to be single isomers, have been assigned the E-configuration, since this configuration facilitates the formation of a stabilising

intramolecular hydrogen bond between the amine proton and the sp^2 nitrogen of the quinazoline ring. Although the nucleophilic displacement of the methylthio groups in ketene S,S-acetals has previously been reported, the compounds obtained from the reaction of (5) or (22) and carbon disulphide/iodomethane were resistant to nucleophilic substitution. For example when the ketene S,S-acetals were heated at reflux temperature with diaminoethane in ethanol or butanol no new products were obtained.

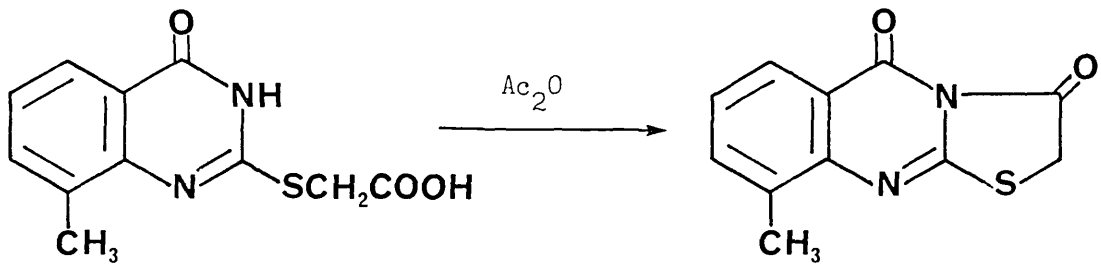
Sulphur Containing Analogues of Deoxyvasicinone

The first example of a sulphur containing derivative of deoxyvasicinone (5) was recorded in 1950. Kendall and Duffin[37] reported that the cyclisation of 3,4-dihydroquinazolin-4-one-2-thiolacetic acid (78), obtained by the reaction of 2-mercapto-3,4-dihydroquinazolin-4-one (76) with chloroacetic acid (77), gave a product which may be represented by structure (79) or (80). (Scheme 20).



Scheme 20

In a reinvestigation of this reaction, Gupta et al[38] demonstrated that structure (79) is in fact correct. The 8-methyl derivative (81) was prepared and cyclised with acetic anhydride to give a single compound (82). (Scheme 21).

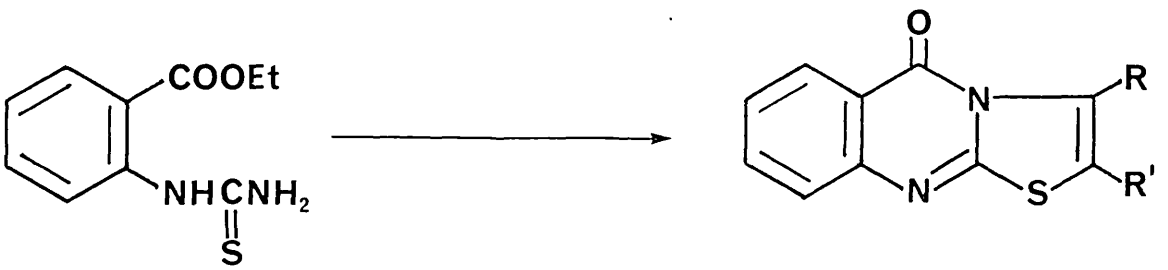


(81) (82)

Scheme 21

Structure (82), and hence structure (79), is correct, since in the proton magnetic resonance spectra the methyl groups of both (81) and (82) appear at δ2.00. If a structure of the type (80) had been formed then the methyl protons would have shown a downfield shift due to the deshielding influence of the carbonyl group of the thiazolidinone ring.

In 1952 Khosla et al[39] described the preparation of substituted thiazolo[2,3-b]-quinazolinones of the type (84) by the condensation of 2-carbethoxyphenylthiourea (83) with α-haloketones. (Scheme 22).

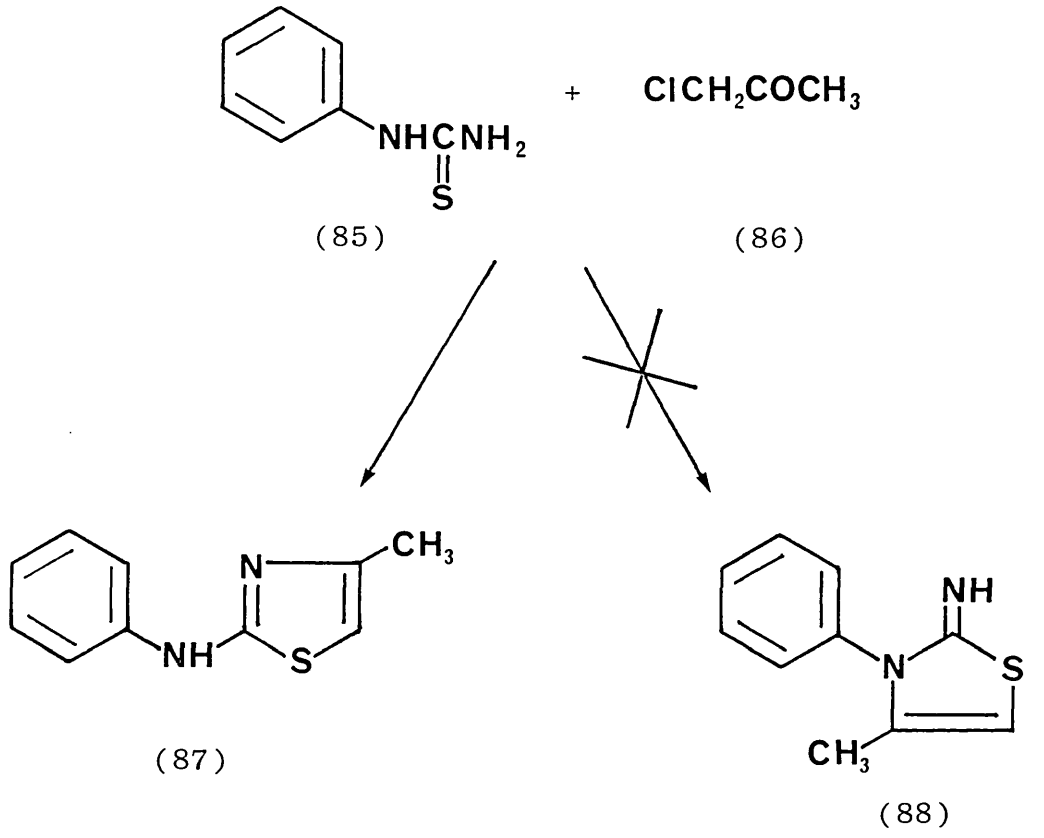


(83) (84)

R	R'
CH_3	H
CH_3	CH_3
CH_3	CO_2Et
Et	H
Ph	H

Scheme 22

These authors discounted the formation of [3,2-a] analogues of the type (80), since condensation of phenylthiourea (85) with chloroacetone (86) gave only (87) and no (88). (Scheme 23).

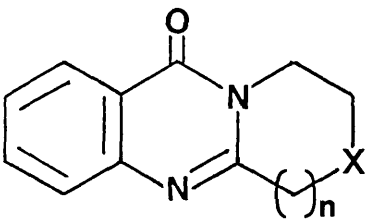


Scheme 23

Since this early work, a number of routes to thiazolo [2,3-b]quinazolinones have been developed and numerous derivatives synthesised and tested for pharmacological activity.

The first example of a fused quinazolinone with a sulphur atom β to the carbon-nitrogen double bond was disclosed in a patent which described the preparation of pharmaceutically active hetero tricyclic compounds of the type (89)[40], including a number of 9-substituted derivatives of (12)(X = S, n = 1), from the reaction of anthranilic

acids with lactim ethers using the method of Peterson and Tietze.

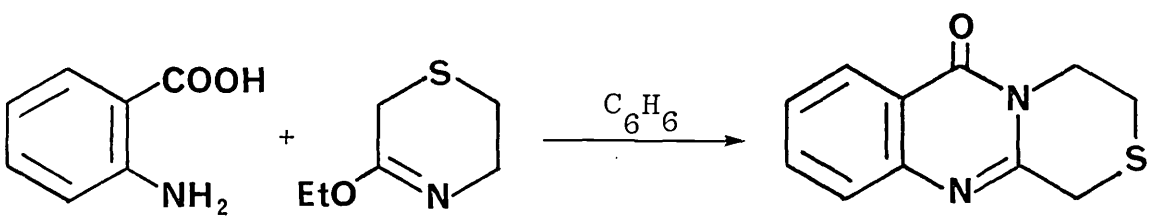


X = O,S or NH

n = 1 or 2

(89)

Later, Bhandari et al[41] described the synthesis of 3,4-dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (12) and its 9-chloro derivative by a similar method. For example when anthranilic acid (24) and 3-ethoxy-Δ^3-thiomorpholine (90) were heated in dry benzene for twelve hours, (12) was obtained. (Scheme 24).

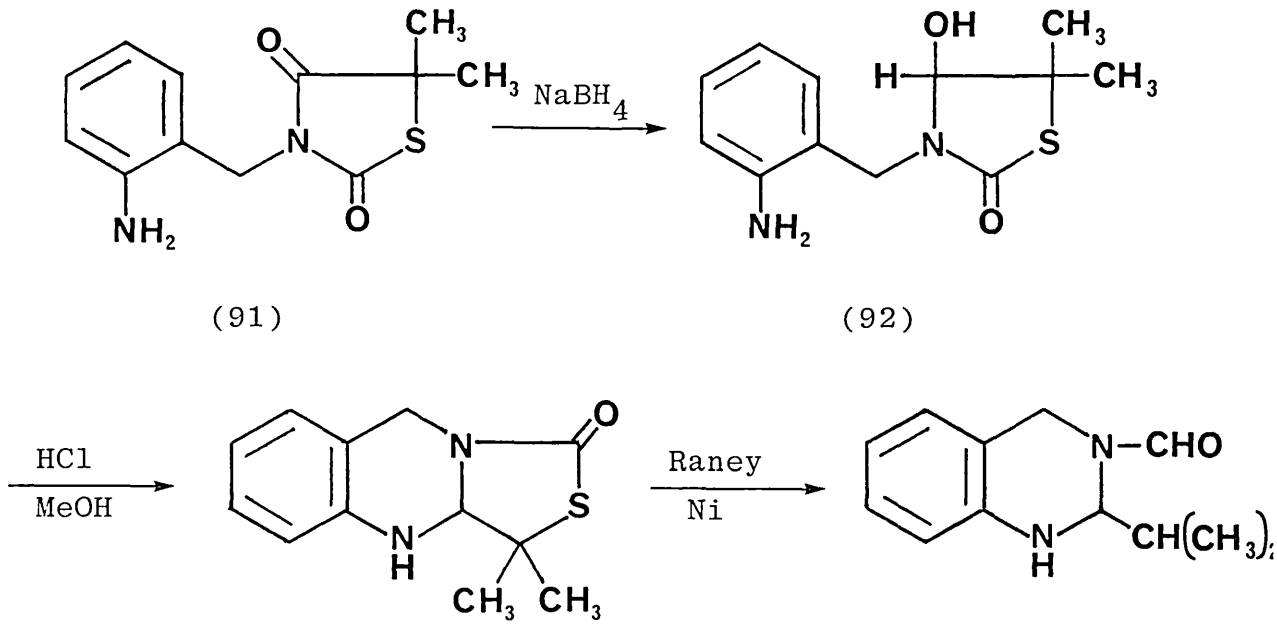


(24) (90) (12)

Scheme 24

The thiazino[3,4-b]quinazolinone (12) was tested for central nervous system, cardiovascular system, anti-inflammatory, anti-arythmic, anti-cholinergic and anti-histamanic activity. However, no noteworthy activity was observed.

The first example of the thiazolo[4,3-b]quinazoline system was reported in 1982 by Speckamp and Hamersma[42]. The quinazoline (93) was obtained following cyclisation of 3-(2-aminobenzyl)-4-hydroxy-5,5-dimethylthiazolidin-2-one (92) (obtained by selective reduction of the intermediate 3-(2-aminobenzyl)-5,5-dimethylthiazolidine-2,4-dione (91) with sodium borohydride) in hot saturated methanolic hydrogen chloride solution[58]. The heterocycle (93) was desulphurised with Raney-nickel to give the novel quinazoline (94). (Scheme 25).



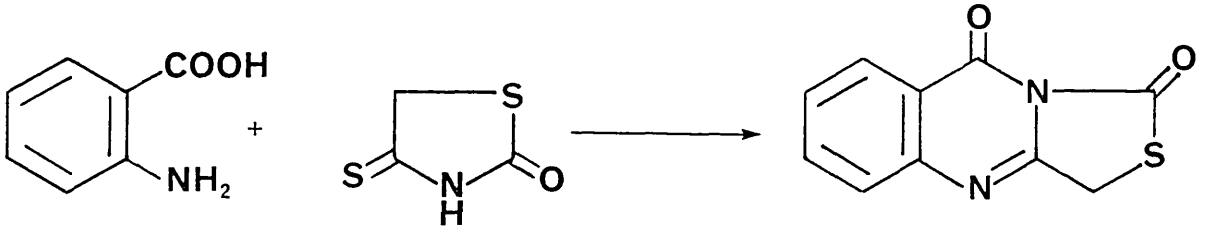
(91) (92)

(93) (94)

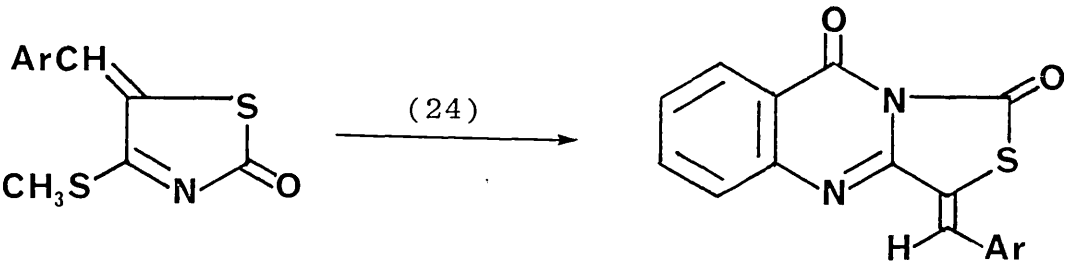
Scheme 25

Shortly afterwards, Daboun and Abdel Aziz[43,44] reported the preparation of thiazolo[4,3-b]quinazoline-1,9-dione (96)

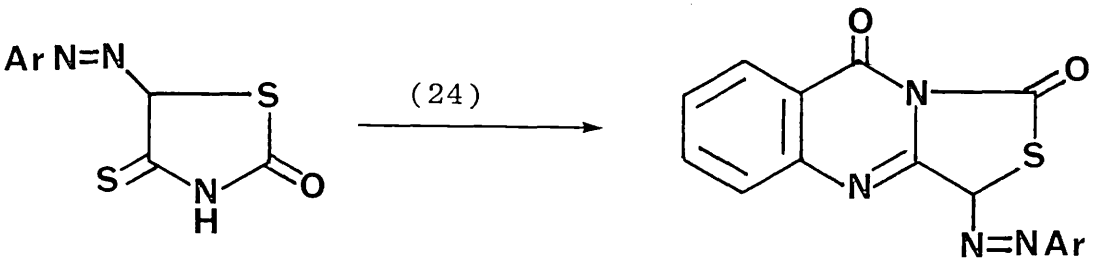
by the condensation of anthranilic acid (24) with 2-thiazolidinone-4-thione (95) in ethanol or glacial acetic acid. These authors had originally intended to synthesise both arylidene (99) and arylazo (100) derivatives by condensation of (96) with aromatic aldehydes and coupling with aryldiazonium salts respectively. However, in both instances the starting material was recovered unchanged. Compounds (99) and (100) were alternatively prepared, in good yield, by the reaction of anthranilic acid (24) with the appropriate substituted thiolactim ether (97) and thiazolidinone thione (98) respectively. (Scheme 26).



(24) (95) (96)



(97) (99)

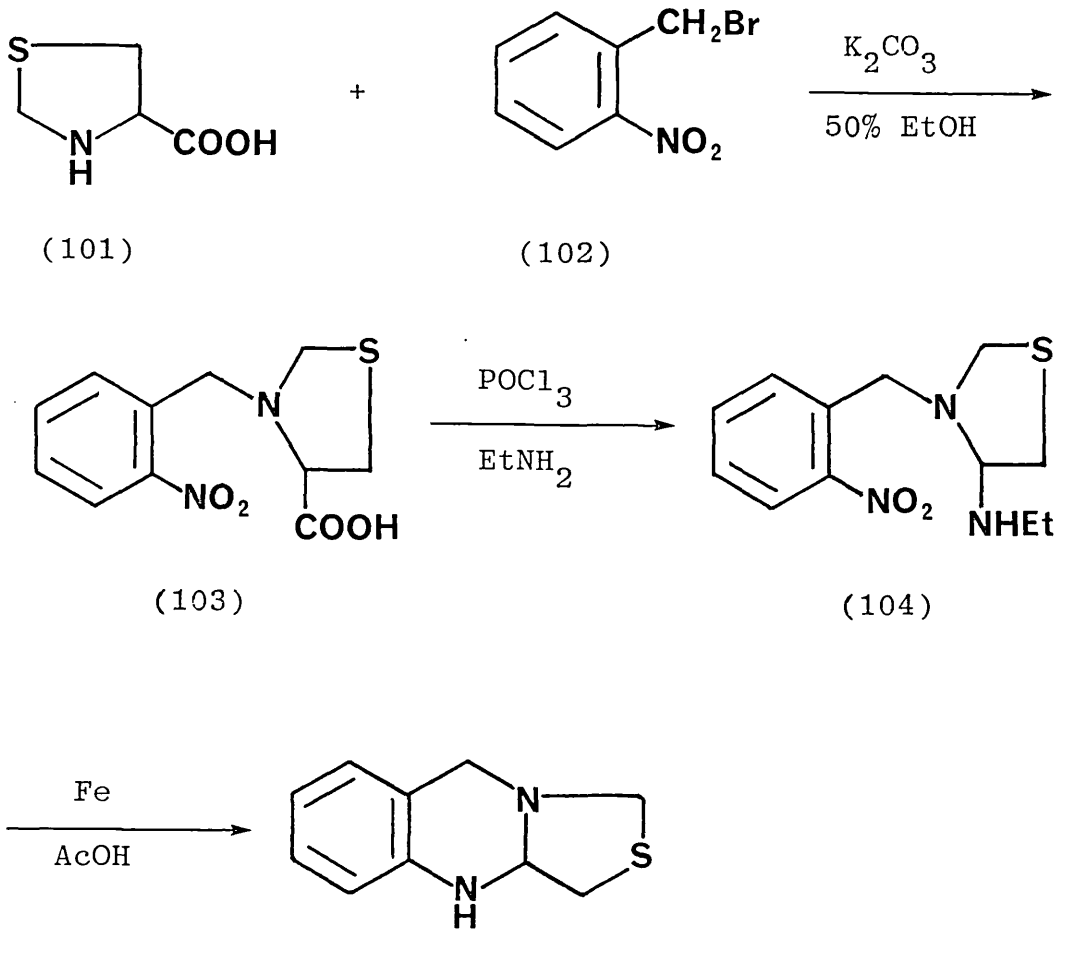


(98) (100)

Scheme 26

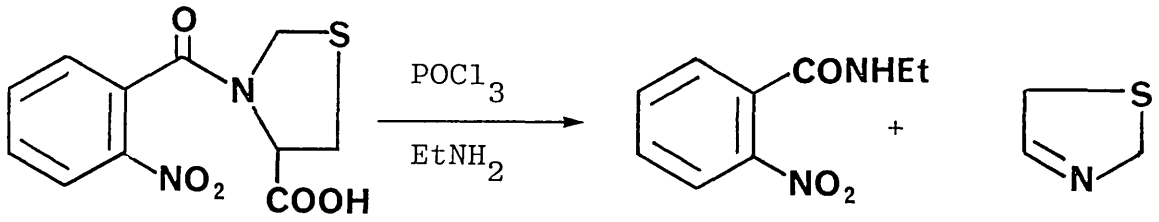
Recently the reduced thiazolo[4,3-b]quinazoline (105) was obtained by a three step process[45]. Treatment of thiazolidine-4-carboxylic acid (101) with 2-nitrobenzylbromide (102) in a 50% aqueous ethanolic

potassium carbonate solution yielded 3-(2-nitrobenzyl)-thiazolidine-4-carboxylic acid (103). Decarboxylation of (103) with phosphoryl chloride, followed by treatment with ethylamine gave 3-(2-nitrobenzyl)-4-ethylaminothiazolidine (104) which was reductively cyclised to the thiazolo[4,3-b]-quinazoline (105) by heating at 130°C with a mixture of glacial acetic acid, iron filings and iron dust. (Scheme 27).



Scheme 27

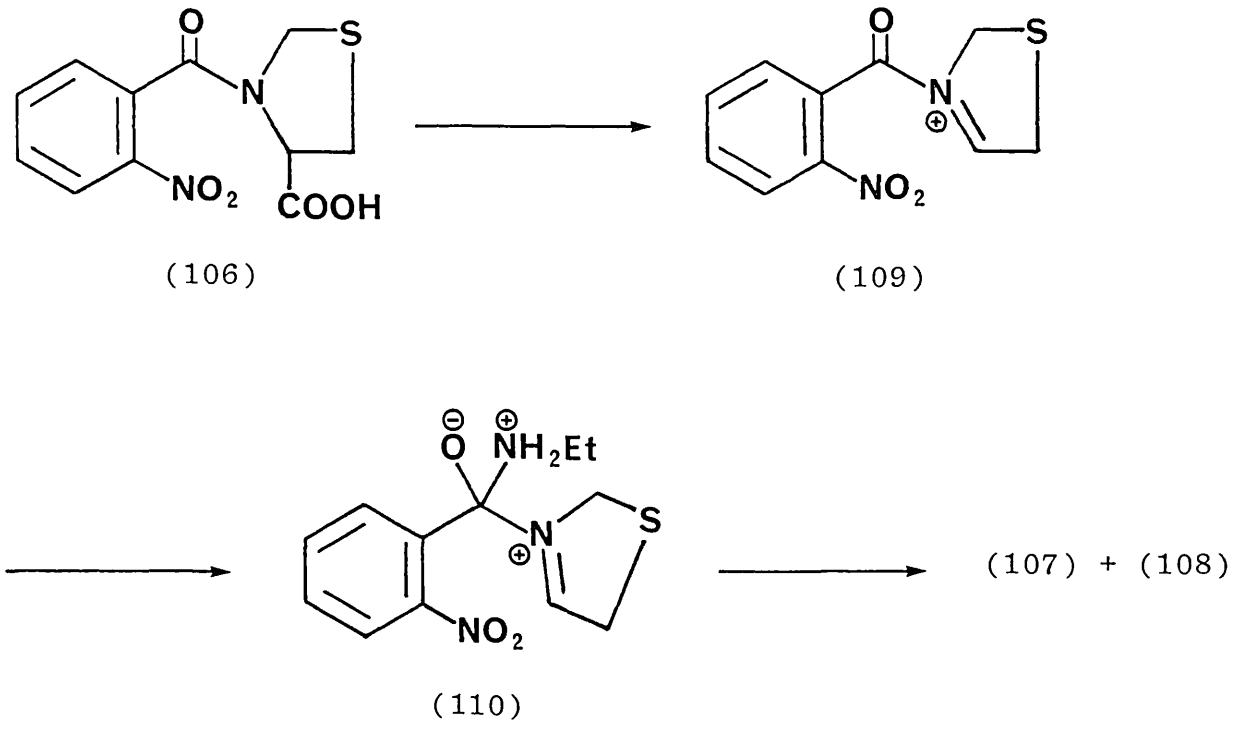
Similar treatment of the benzoyl derivative (106) failed to realise any tricyclic compound. Treatment of this compound with phosphoryl chloride, followed by quenching in ethylamine produced only the arylamide (107) and 5H-thiazole (108). (Scheme 28).



(106) (107) (108)

Scheme 28

It was proposed that the reaction proceeds via the iminium ion (109), produced by decarboxylation of (106) in the presence of the Lewis acid, phosphoryl chloride. However, since the carbonyl carbon is more electrophilic than the ring carbon α to the thiazolidinium nitrogen, preferential attack of the nucleophile at the carbonyl carbon occurs to give the intermediate (110). The nitroamide (107) and thiazole (108) result on collapse of this intermediate. (Scheme 29).



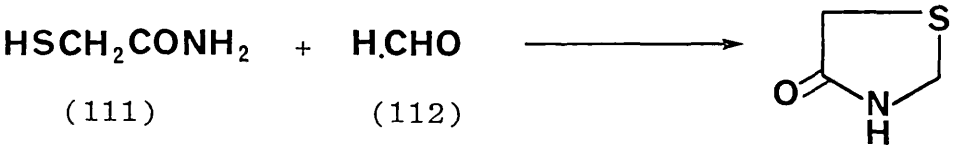
Scheme 29

A comprehensive survey of the literature revealed that no examples of thiazolo[4,3-b]quinazolin-9-one (11) or 1,4-thiazepino[3,4-b]quinazolin-7-one (13) have been reported.

Sulphur Containing Lactams

Although numerous derivatives of 4-thiazolidinone have been prepared, a comprehensive literature search indicated only two routes to 4-thiazolidinone (113) itself.

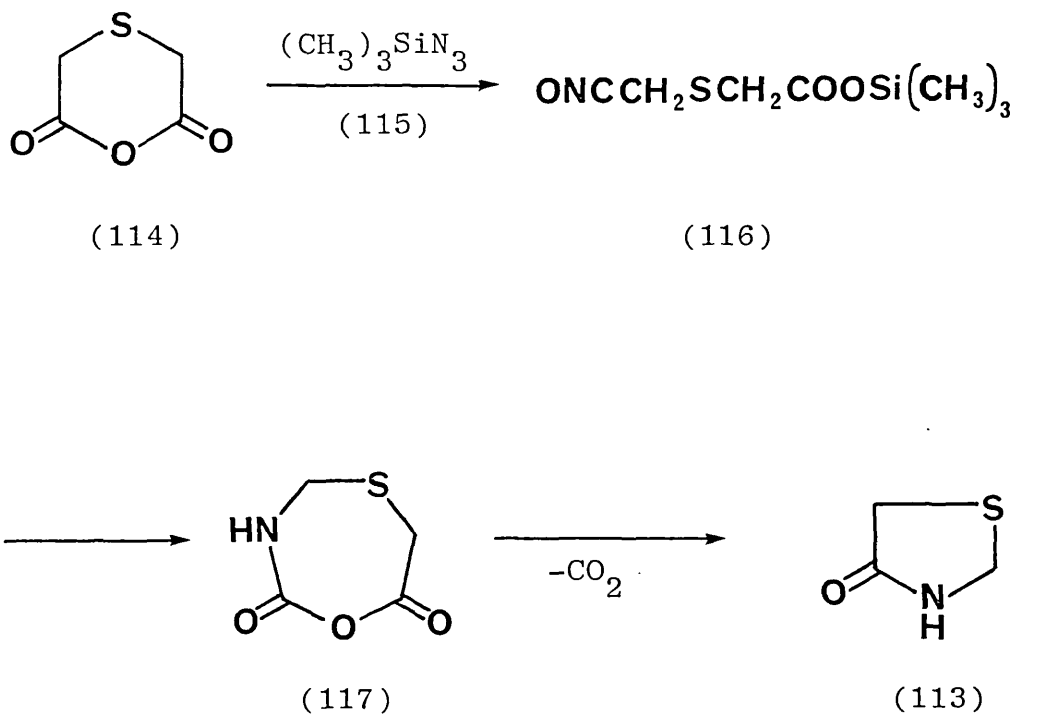
In 1956 Japanese workers[46] prepared 4-thiazolidinone (113), in 49% yield, by the condensation of mercaptoacetamide (111) and formalin (112). (Scheme 30).



(111) (112) (113)

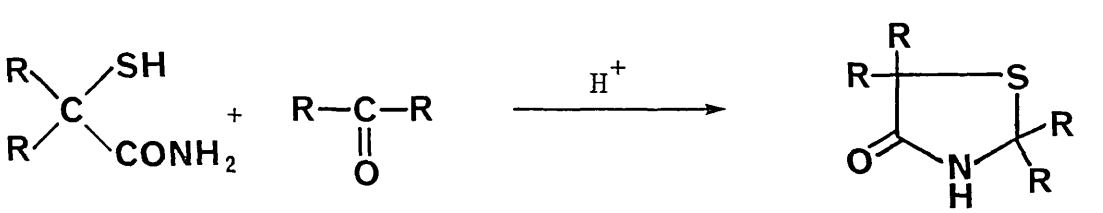
Scheme 30

More recently, Krickeldorf[47] prepared 4-thiazolidinone (113), in 43% yield, by ring contraction of an intermediate 4-aminocarboxylic acid N-carboxylic anhydride (117). The 4-aminocarboxylic acid N-carboxylic anhydride (117) was prepared by mild hydrolysis of the trimethylsilyl ester (116), obtained by the reaction of trimethylsilylazide (115) with the cyclic 1,3-dicarboxylic acid anhydride (114). (Scheme 31). The same author also prepared 2,2-dimethyl- and 2,5-dimethyl-4-thiazolidinone by this route.



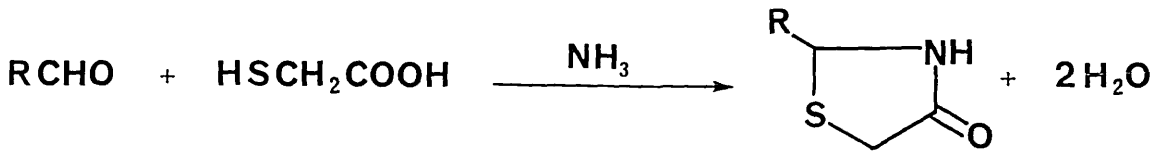
Scheme 31

4-Thiazolidinones, substituted at position 2 or 5, were prepared by Skinner and James[48] by the reaction of α,α-dialkyl-α-mercaptoamides with a variety of carbonyl reagents in the presence of mineral acids. (Scheme 32).



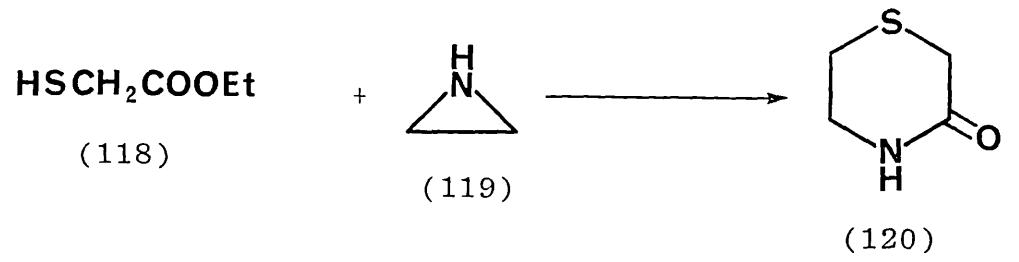
Scheme 32

Surrey and Cutler[49] have also described the preparation of 4-thiazolidinones substituted at position 2 by heating a mixture of an aldehyde or ketone with thioglycolic acid and ammonia (or an ammonium salt) in benzene with azeotropic distillation of water from the reaction mixture. (Scheme 33).



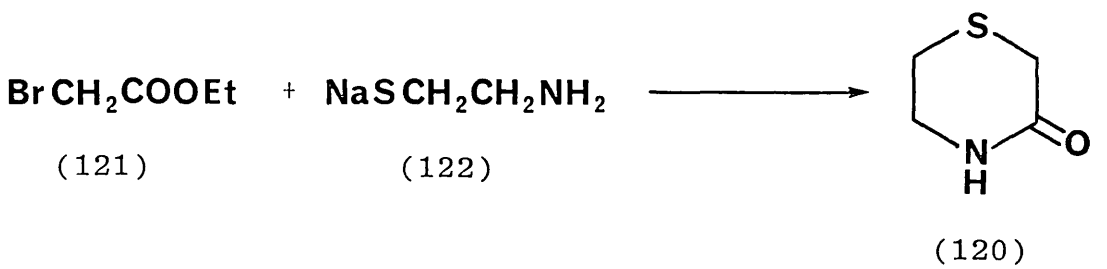
Scheme 33

The six membered sulphur containing lactam, 3-oxothiomorpholine (120) was first prepared in 1950[50] by the condensation of ethylenimine (aziridine) (119) with ethyl thioglycolate (118). (Scheme 34).



Scheme 34

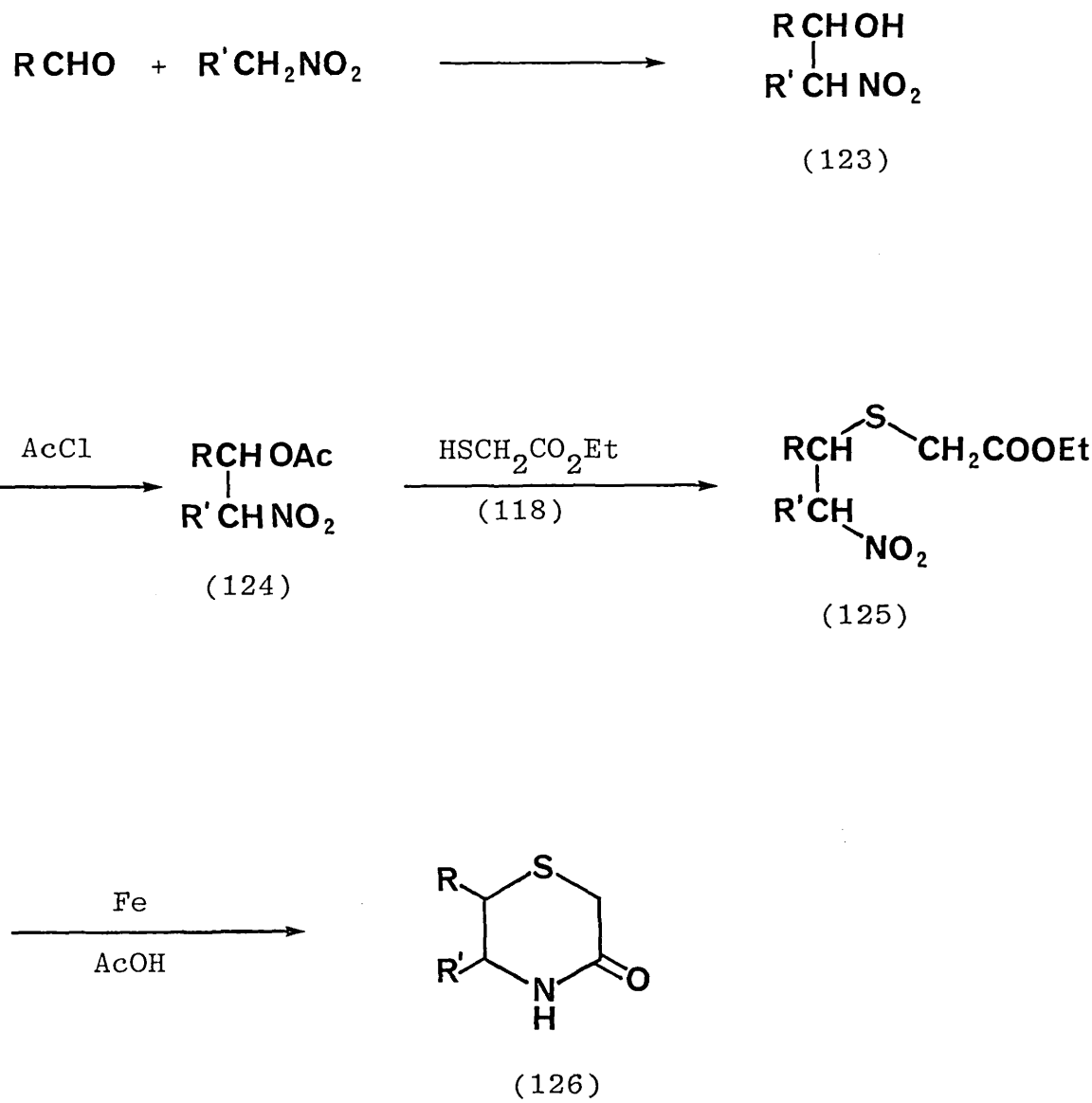
Babichev and Shokol[51] have also reported the preparation of 3-oxothiomorpholine (120), by reaction of ethyl bromoacetate (121) with $NaSCH_2CH_2NH_2$ (122). (Scheme 35).



(120)

Scheme 35

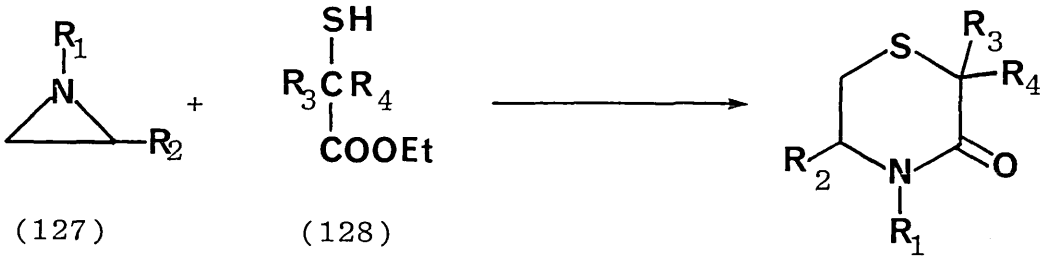
A number of 2,4,5 or 6- substituted derivatives of 3-oxothiomorpholine have been reported by Lehr et al[52]. Condensation of ethyl thioglycolate (118) with acetylated nitroalkanols (124), (prepared by the acetylation of the alkanols (123), obtained on reaction of carbonyl compounds with the anions of nitroalkanes) followed by reductive cyclisation of the resulting ethyl nitroalkylmercapto acetates (125), yielded 3-oxothiomorpholines substituted at positions 6, or 5 and 6 (126). (Scheme 36).



Scheme 36

Homologues of ethyl thioglycolate with one or two alkyl groups at the α position also condense with acetylated nitroalkanols to give nitromercapto esters. However, reductive cyclisation of these compounds was unsuccessful.

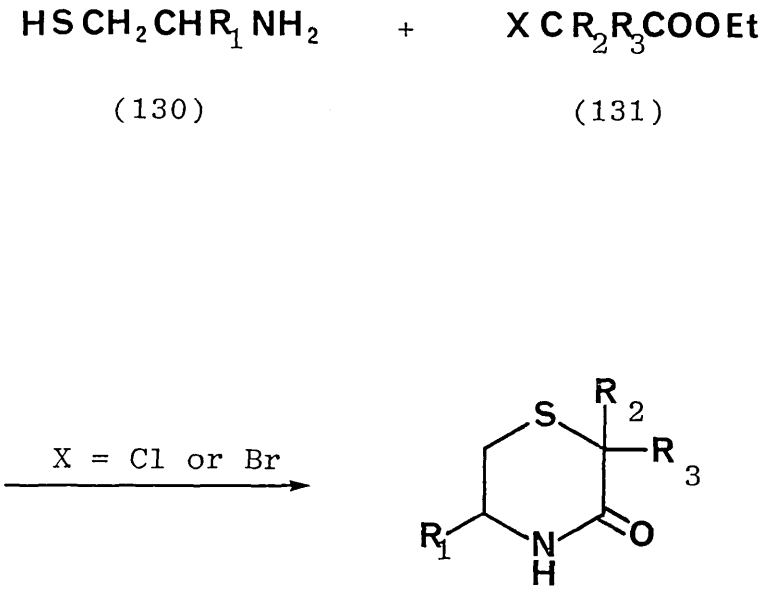
The same authors also prepared analogues of (120), substituted at position 2, 4 or 5 (129) by the reaction of α-mercaptoesters (128) with aziridine derivatives (127). (Scheme 37).



(127) (128) (129)

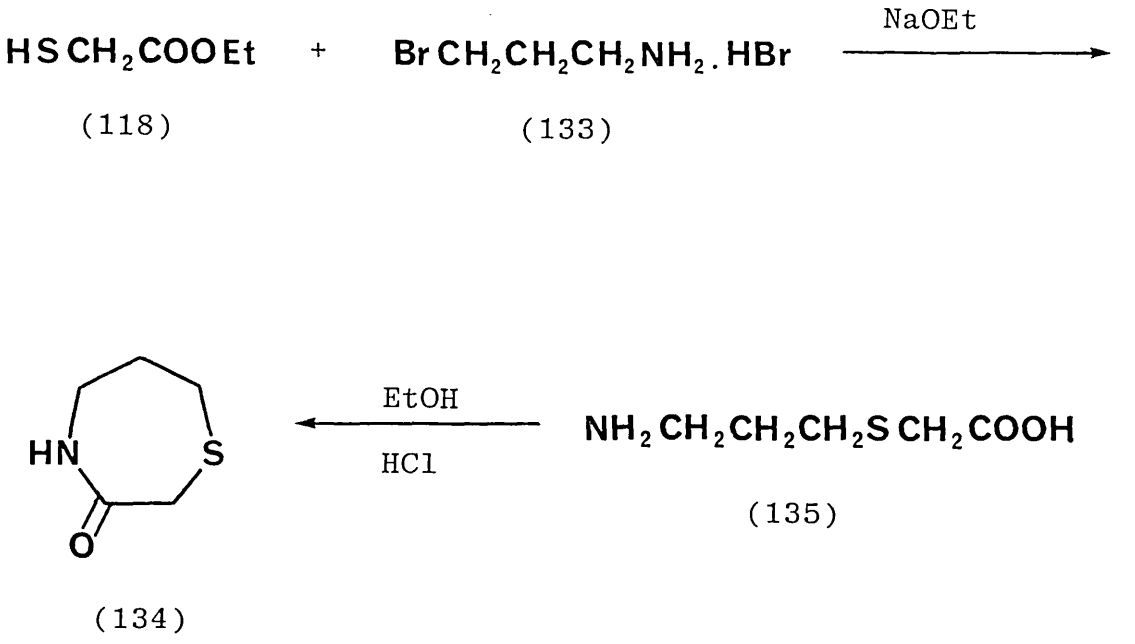
Scheme 37

In cases where the α-mercaptoesters (128) were difficult to obtain, 3-oxomorpholines substituted at positions 2 and/or 5 (132) were alternatively prepared by condensation of α-haloesters (131) with β-mercaptoalkylamines (130). (Scheme 38).



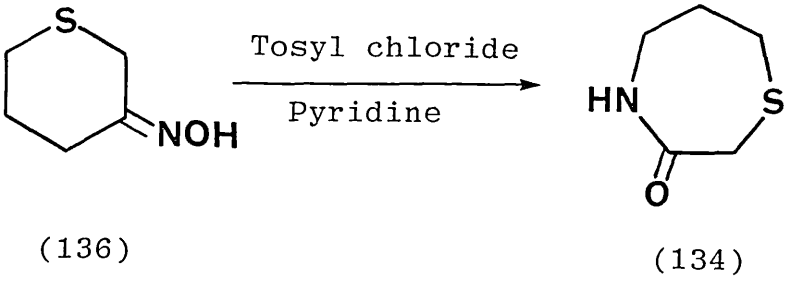
Scheme 38

Like 4-thiazolidinone (113), there are very few examples of routes to 1,4-thiazepin-3-one (134). The seven membered heterocycle (134) was obtained by Rabinovich et al[53] on treating ethyl thioglycolate (118) with sodium ethoxide, followed by 3-bromopropylamine hydrobromide (133). The same authors also obtained (134) by the ring closure of $NH_2(CH_2)_3SCH_2CO_2H$ (135) in ethanolic hydrogen chloride. (Scheme 39).



Scheme 39

1,4-Thiazepin-3-one (134) has also been isolated as a minor product (11%) from the tosyl chloride/pyridine catalysed Beckmann rearrangement of the oxime (136)[54]. (Scheme 40).



Scheme 40

Pummerer Rearrangements

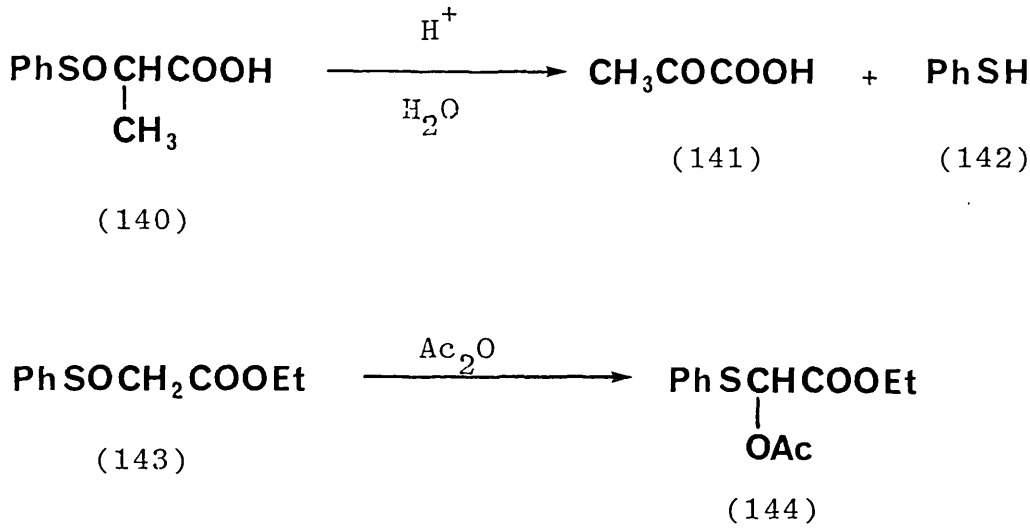
Under the influence of an acidic catalyst, a sulphoxide can be transformed to an α-substituted sulphide, the overall result of the reaction being the reduction of the sulphoxide group and oxidation of the adjacent carbon atom. Because of the pioneering work of Pummerer this transformation has become known as the Pummerer rearrangement.

The earliest example of this type of reaction was in 1909 when Smythe[55] noted that heating benzyl sulphoxide (137) with aqueous hydrochloric or acetic acid led to the formation of benzyl mercaptan (138) and benzaldehyde (139). (Scheme 41).

$$\underset{(137)}{PhCH_2SOCH_2Ph} \xrightarrow[\text{aq. AcOH}]{\text{aq. HCl or}} \underset{(138)}{PhCH_2SH} + \underset{(139)}{PhCHO}$$

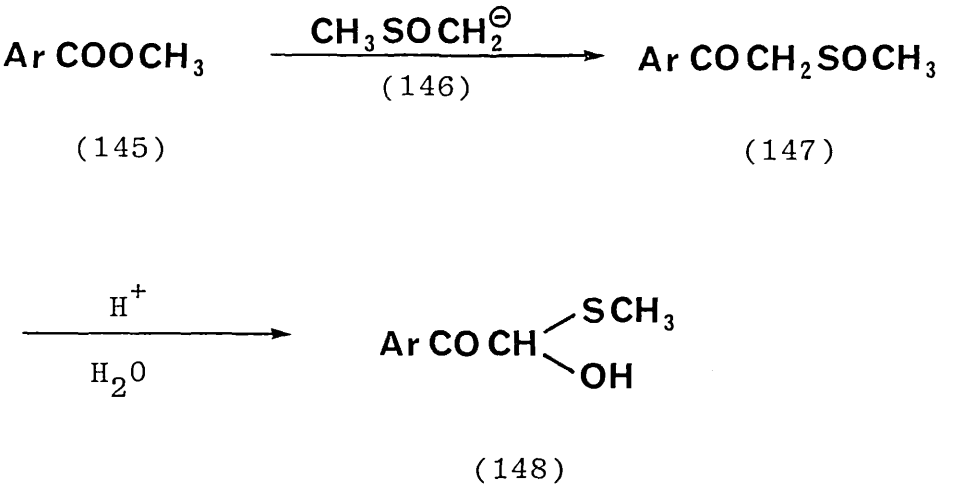
Scheme 41

Shortly thereafter, Pummerer[56,57] reported the acid catalysed cleavage of α-(phenylsulphinyl)propionic acid (140) to thiophenol (142) and pyruvic acid (141), and the acetic anhydride induced rearrangement of ethyl phenylsulphinylacetate (143) to ethyl α-phenylthio-α-acetoxyacetate (144). (Scheme 42).



Scheme 42

Sulphoxides such as β-disulphoxides, β-ketosulphoxides, β-sulphenyl esters/acids and benzylic or allylic sulphoxides appear to be particularly susceptible to this rearrangement with short exposure to acids sufficient to cause reaction. For example, the β-ketosulphoxides (147), obtained from the reaction of methyl sulphinyl carbanion (146) with aromatic esters (145), rearrange to hemi-thioacetals (148) during isolation[59]. (Scheme 43).



(145) (146) (147) (148)

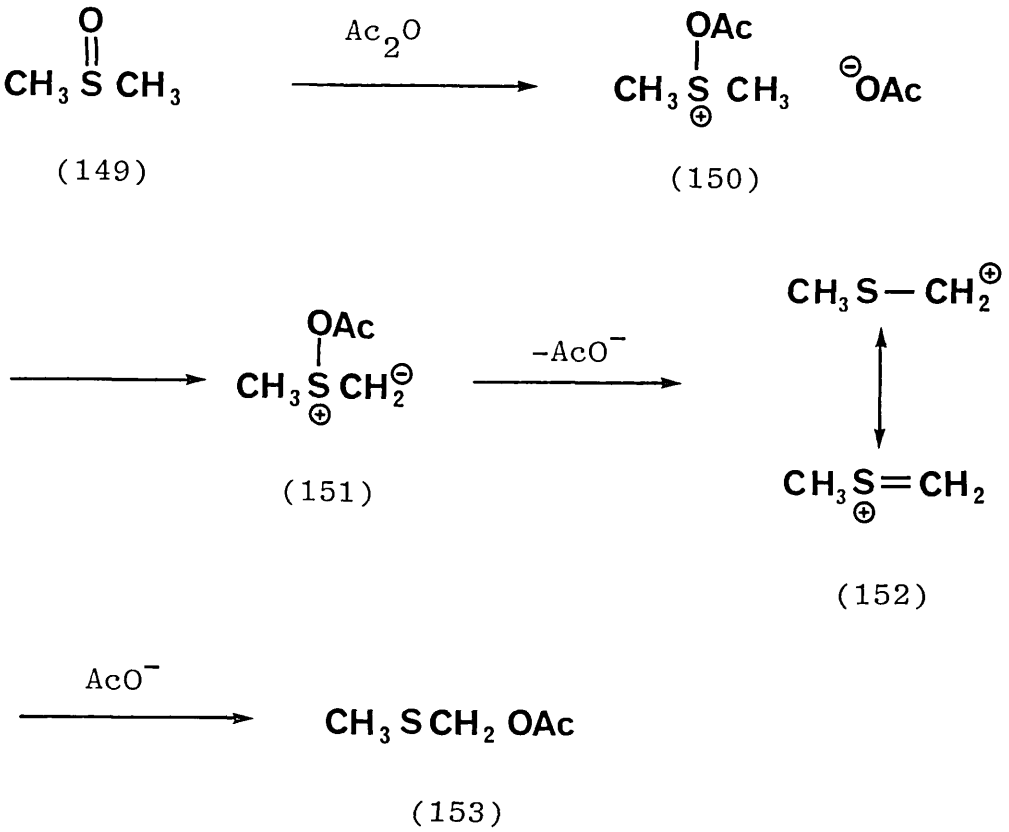
Scheme 43

Simple dialkyl sulphoxides are considerably more stable but can be induced to undergo Pummerer type reactions in the presence of strongly electrophilic reagents such as carboxylic acid anhydrides, acid chlorides, organic sulphur acid chlorides and various phosphorus chlorides and oxychlorides[60].

The mechanism of the Pummerer rearrangement has been the subject of a number of investigations[61]. The acetic anhydride induced rearrangement has been studied in greatest detail, and a discussion of its mechanism will, for the most part, suffice for rearrangements induced by other reagents.

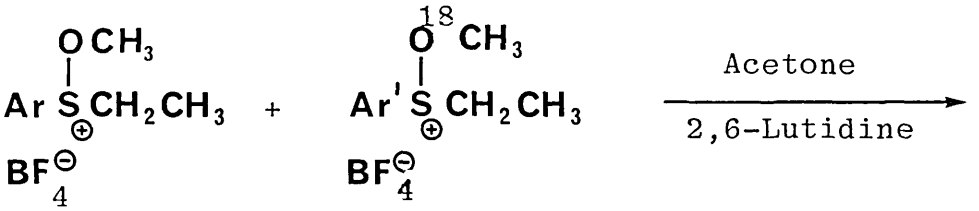
Little doubt exists that the first step in the reaction of a sulphoxide, for example dimethyl sulphoxide (149), with

acetic anhydride is the formation of the acetoxysulphonium salt (150). The details of the rearrangement from (150) to acetoxymethyl methyl sulphide (153) has been the subject of much discussion. Current evidence favours conversion of the acetoxysulphonium salt (150) to an ylide (151), which rapidly eliminates acetate ion to form the resonance stabilised sulphenium ion (152). Reaction of (152) with acetate leads to the observed α-acetoxy sulphide (153). (Scheme 44).

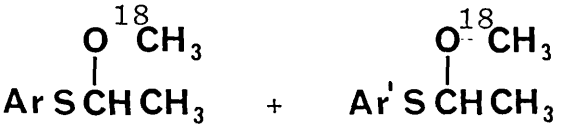


Scheme 44

Cross-over experiments, involving the Pummerer type rearrangement of methoxysulphonium salts, are in agreement with this proposed mechanism. Simultaneous rearrangement of (154) and the O^{18} labelled salt (155) yielded products which indicated that considerable cross-over had occurred, and provided evidence that the alkoxy group exchanged into the medium during the rearrangement. (Scheme 45).



(154) (155) 1389 cpm/mol

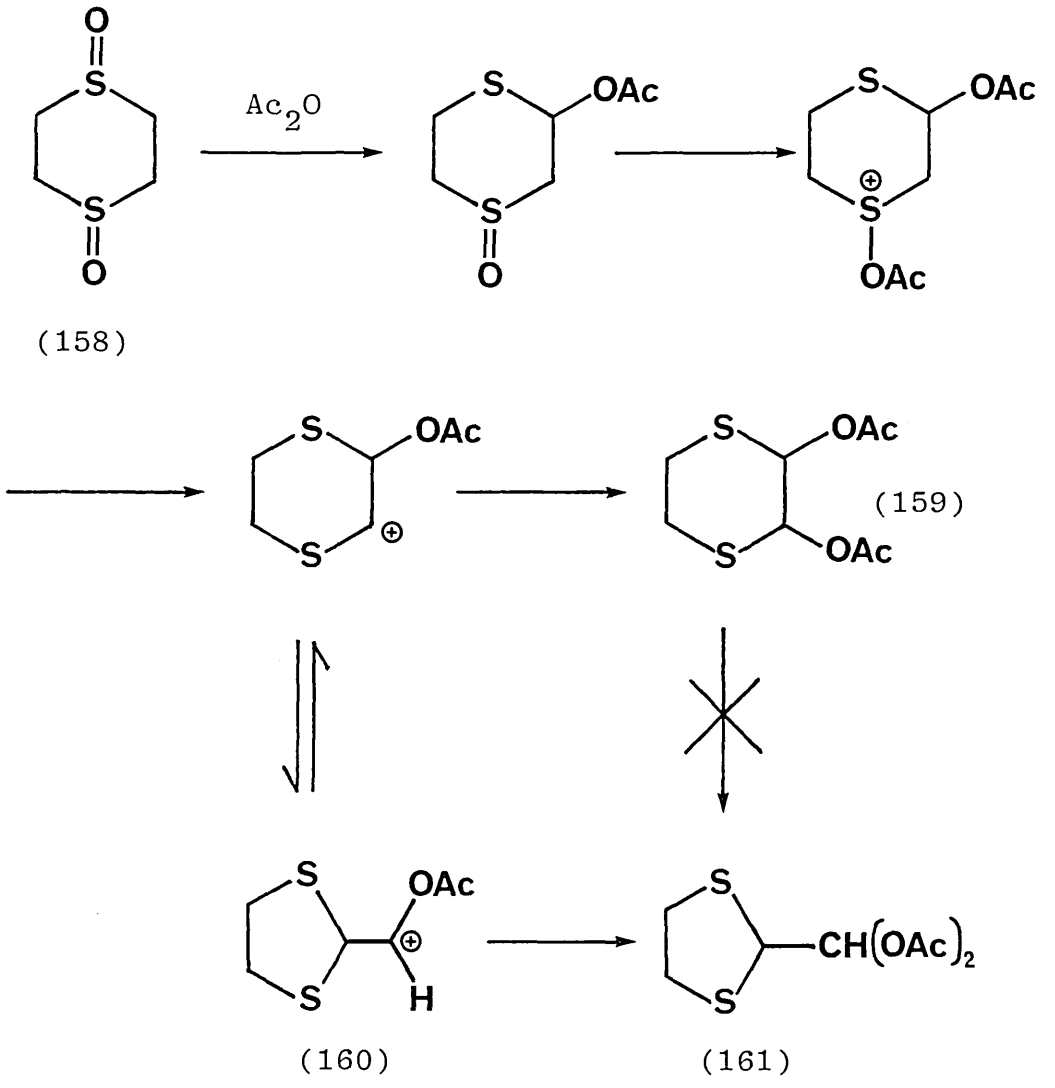


(156) 423 cpm/mol (157) 999 cpm/mol

Scheme 45

Evidence for the intermediacy of α-thiocarbocations in Pummerer rearrangements was provided in 1963 by Parham et al[616]. The reaction of the disulphoxide (158) with acetic anhydride results in the formation of two products, (159) and (161). Under experimental conditions the conversion of (159) to (161) could not be induced. It therefore follows that (161) can only result from the

rearranged acetate (160). (Scheme 46).



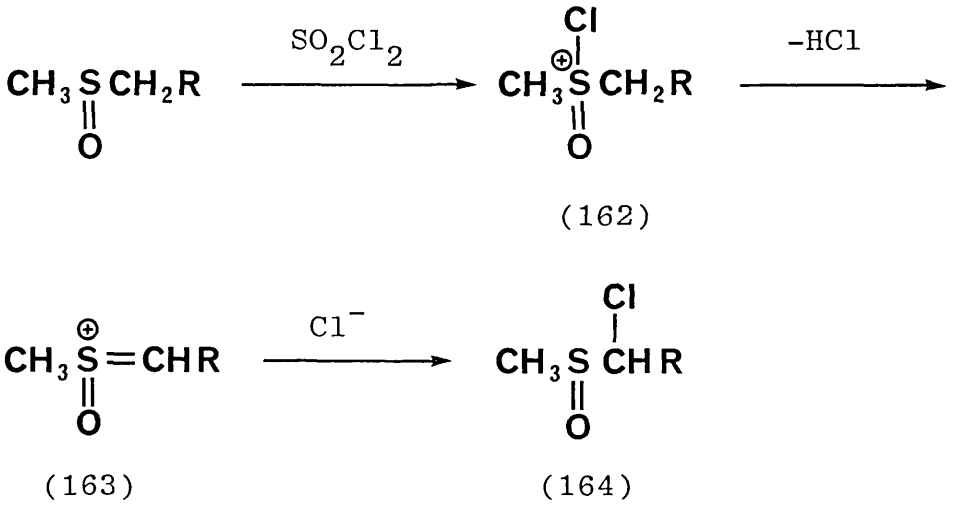
Scheme 46

Further evidence for the intermediacy of resonance stabilised carbocations in the Pummerer rearrangement has been provided by Meerwein, who isolated the relatively stable ion (152) as its hexachloroantimonate salt[63].

Halogenation of Sulphoxides and Sulphides

Sulphoxides having at least one hydrogen on the α-carbon can be converted into α-halogenosulphoxides by electrophilic halogenating agents, eg NCS[64], SO_2Cl_2[65], NOCl[66], Br_2[67], TsCl[68] etc.

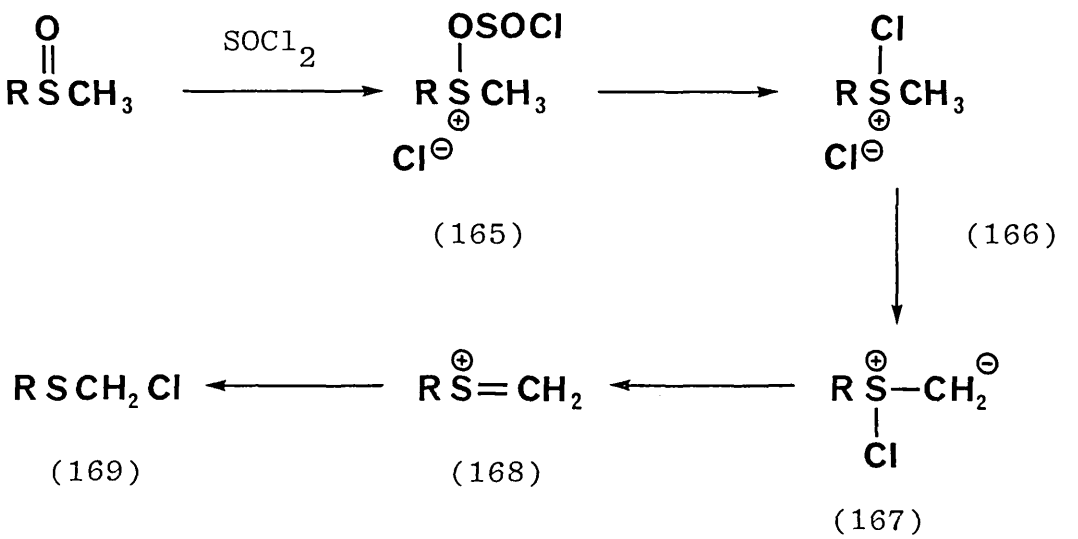
The reaction mechanism has been shown to involve formation of a halo-oxosulphonium ion (162) which loses hydrogen chloride under the influence of a base present in the medium to give the oxosulphenium ion (163). Addition of halide ion to this intermediate furnishes the final product (164). (Scheme 47).



Scheme 47

The reaction of sulphoxides with thionyl chloride or acyl halides[69] leads to α-chlorosulphides, the formation of which may be explained by a Pummerer type reaction. The reaction

is believed to proceed by initial displacement of a chloride ion from thionyl chloride or the acyl chloride by the nucleophilic sulphoxide oxygen. The resulting sulphoxonium salt (165) may decompose to the chlorosulphonium salt (166) and subsequently form the product (169) via the intermediates (167) and (168). (Scheme 48).

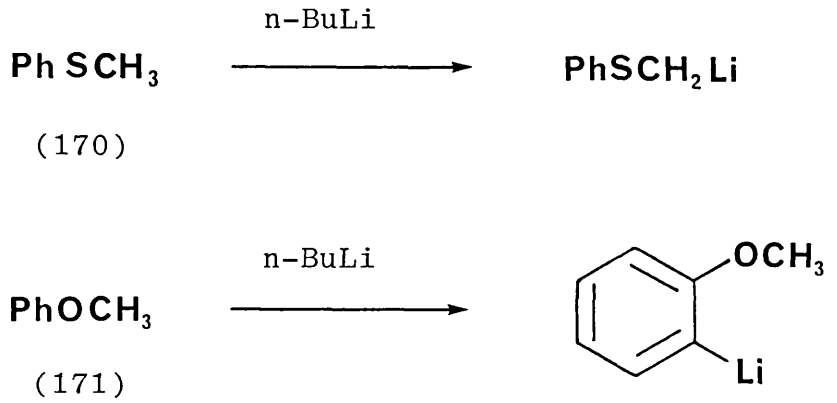


Scheme 48

Preparations of α-halogenoalkyl sulphides from alkyl sulphides mostly involve straightforward reagents such as SCl_2, SO_2Cl_2, NCS etc. The reaction mechanism is thought to involve formation of a chlorosulphonium salt of the type (166) followed by decomposition to the α-chlorosulphide along the pathway (166) - (169), previously outlined in Scheme 48.

The Nature of Carbanion Stabilisation by Sulphur

There is substantial evidence, of both a qualitative and quantitative nature, supporting the view that α-hydrogens in sulphides (as well as higher valent organosulphur compounds) are more acidic than α-hydrogens in ethers or other compounds involving only first row elements. For example, in 1940 Gilman[70] reported that while thioanisole (170) could be metalated at the methyl group, anisole (171) underwent only nuclear metalation. (Scheme 49).



Scheme 49

This cannot be rationalised on the basis of inductive effects since oxygen is more electronegative than divalent sulphur. The much higher acidity of C-H bonds α to sulphur as compared to C-H bonds α to oxygen or in hydrocarbons has usually been ascribed to dπ to pπ back bonding of the carbanion lone pair into the vacant 3d orbital of the

sulphur. However the relevance of d orbital conjugation to ground state properties of organosulphur compounds has been challenged on the basis of molecular orbital calculations by Wolfe and co-workers[71-73]. For example, molecular orbital calculations on $RSCH_2^-$ and $RCH_2CH_2^-$ (R = H or CH_3) predict the order of gas phase carbanion stability as S > O > C whether or not sulphur 3d orbitals are used in the calculations. Indeed, in the calculation of proton affinities of these anions (inversely proportional to carbanion stability), the inclusion of d orbitals has essentially no effect on the numbers obtained. The other conclusions which Wolfe drew from these molecular orbital calculations were -

(i) The C-S bond in $^-CH_2SH$ is longer than in CH_3SH which argues against d-p π bonding (since bond shortening should occur if π bonding is involved).

(ii) An important mechanism of stabilisation of carbanions by adjacent sulphur is by polarisation of the electron distribution ie dispersal of the charge over the molecule.

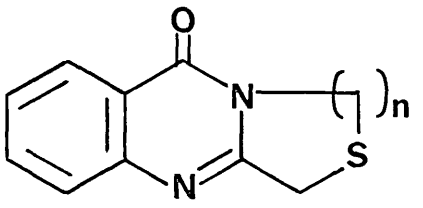
DISCUSSION

Discussion

Preparation of Sulphur Containing Quinazolinones

The synthesis and reactions of deoxyvasicinone (5) and its higher pyrido and azepino analogues have previously been extensively examined (see Introduction). However, as previously noted, there are very few examples of thiazolo-, thiazino- or thiazepinoquinazolinones of the type (11), (12) and (13), and consequently their chemistry has been little investigated.

This thesis presents an account of the synthesis of the heterocycles (11) - (13) and examines certain areas of their chemistry, with a view to preparing new derivatives for pharmacological screening, or intermediates for use in the synthesis of novel ring systems.



(11) n = 1

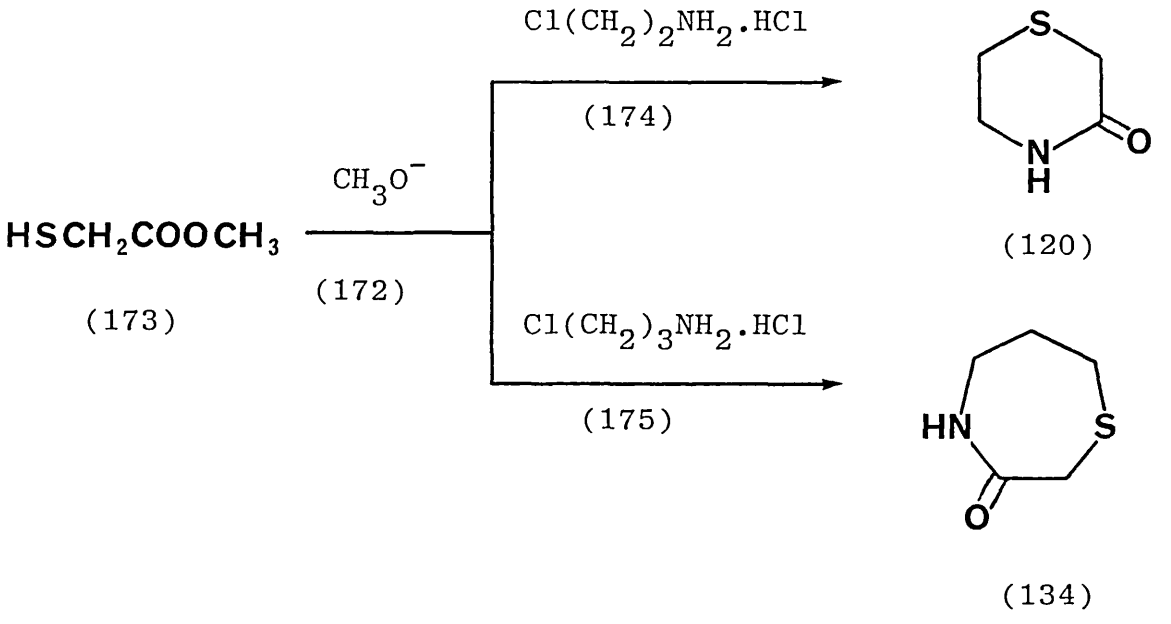
(12) n = 2

(13) n = 3

The most obvious route to the compounds (11) - (13) is by the condensation of anthranilic acid (24) with the appropriate sulphur containing lactams, using the method of Shakhidoyatov[14].

The lactams required for this study, namely 4-thiazolidinone (113), 3-oxothiomorpholine (120) and 1,4-thiazepin-3-one (134) were not commercially available and required to be synthesised.

Both the six and seven membered lactams, (120) and (134), were conveniently prepared using a modification of the method described by Rabinovich et al[53], from 2-chloroethylamine hydrochloride (174) and 3-chloropropylamine hydrochloride (175) respectively. (Scheme 50).



Scheme 50

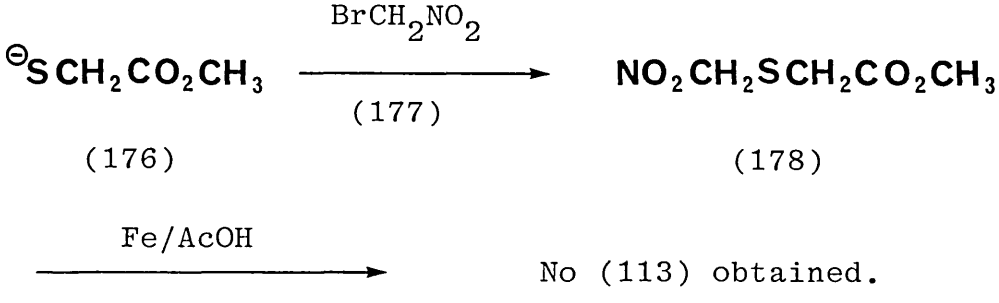
4-Thiazolidinone (113), on the other hand, proved much more difficult to prepare. Of the two literature methods

available for the synthesis of this compound, only one appeared to be applicable for large scale synthesis, namely by the reaction of thioglycolamide (111) and formalin[46]. (See Scheme 30, p 50). Unfortunately this did not prove to be the case. Concentration of the reaction mixture in vacuo, followed by vacuum distillation of the resulting viscous syrup afforded the lactam (113), albeit in low yield. We believe the low yield of this reaction is due to extensive thermal decomposition during the distillation stage, which made it extremely difficult and time consuming to produce 4-thiazolidinone (113) in the quantities required for further reactions. Attempts to isolate the desired compound (113) from the reaction mixture, prior to vacuum distillation, by solvent extraction using a variety of solvents (eg ethyl acetate, dichloromethane, acetone) proved unsuccessful. It therefore seems probable that the lactam (113) is actually formed by either thermal dehydration or thermal depolymerisation of some intermediate species during the process of vacuum distillation.

As a result we have examined a number of alternative routes for the synthesis of 4-thiazolidinone (113).

The initial strategy employed involved replacement of formalin with paraformaldehyde in dry benzene, and acid catalysed condensation of this reagent and thioglycolamide (111), with azeotropic removal of the water produced during the reaction. No products were obtained using this method.

The synthesis of sulphur containing lactams by the reductive cyclisation of nitroesters has previously been described by Lehr et al[52]. In an attempt to prepare 4-thiazolidinone (113) by a similar method, the nitroester (178) was prepared by the reaction of bromonitromethane[74] (177) with the anion derived from methyl thioglycolate (176). Attempted reductive cyclisation of the nitroester (178) with a mixture of reduced iron powder and glacial acetic acid failed to realise any 4-thiazolidinone (113). (Scheme 51).

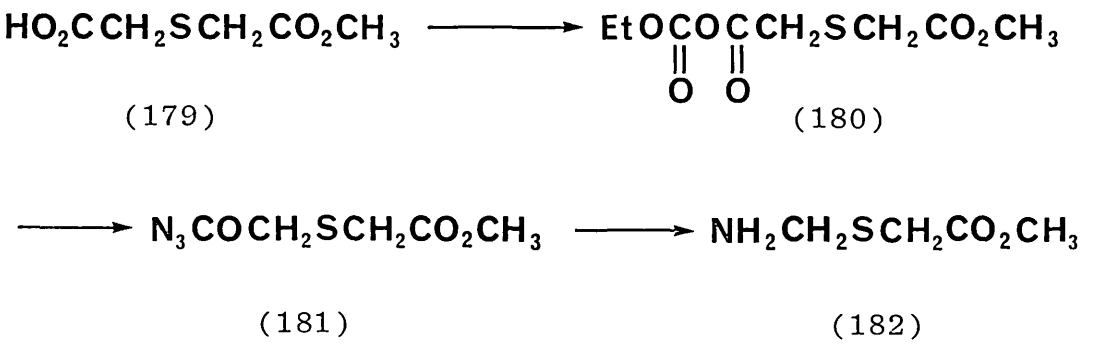


Scheme 51

The fate of the nitroester (178) in this reaction was not investigated further, although a strong smell of hydrogen sulphide was detected during the course of the attempted reduction.

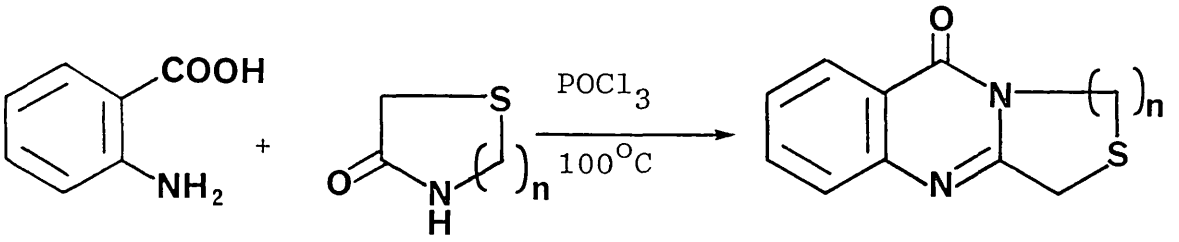
A final attempt at preparing the lactam (113) involved conversion of the acid/ester (179) (prepared from chloroacetic acid and methyl thioglycolate) to the mixed anhydride (180) by treatment with ethyl

chloroformate/triethylamine. It was hoped that (180) could be converted to the carbonyl azide (181) which could be induced to undergo a Curtius rearrangement to yield the intermediate amine (182). The latter compound would be subject to a rapid ring closure with subsequent formation of (113). (Scheme 52). Unfortunately, this route also proved unsuccessful, and attempts to prepare (113) by alternative synthetic routes were abandoned.



Scheme 52

When a mixture of anthranilic acid (24) and the lactams (113), (120) or (134) was heated at 100°C in the presence of phosphoryl chloride, the fused quinazolinones, (11)-(13) were isolated in good yield. (Scheme 53).



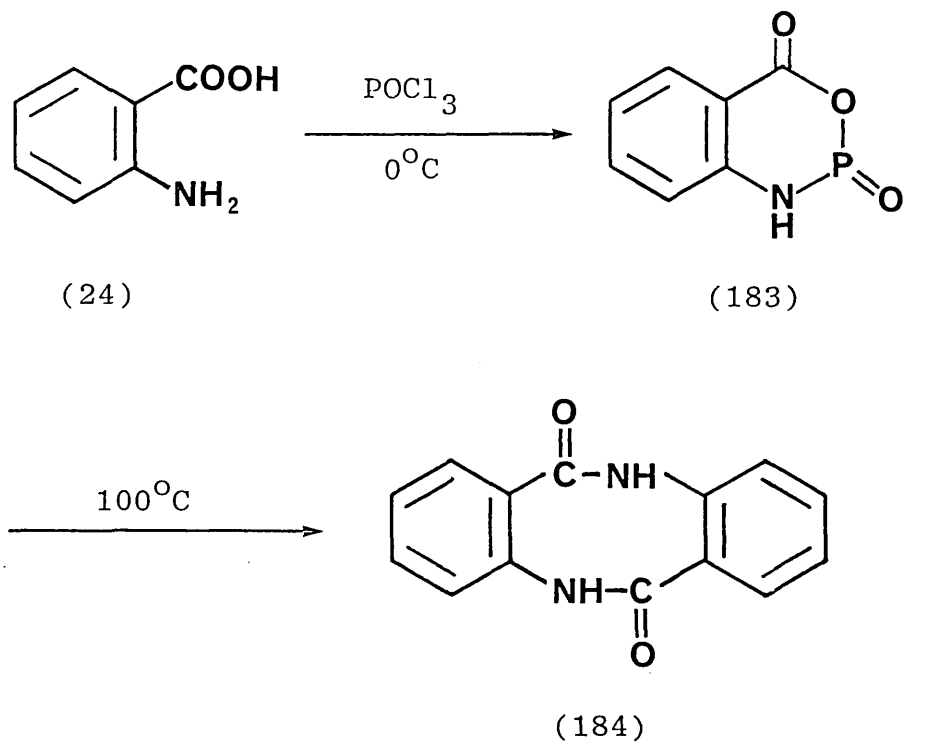
(24) (113) n = 1 (11) n = 1

(120) n = 2 (12) n = 2

(134) n = 3 (13) n = 3

Scheme 53

The compounds (11)-(13), prepared by the aforementioned technique, had analytical and spectroscopic data which was consistent with their proposed structure. Although this reaction is a relatively simple one step process, the yields of quinazolinone were reduced for two main reasons. Firstly, the relatively vigorous reaction conditions almost certainly resulted in some thermal decomposition of the reactants and/or products. Secondly, anthranilic acid (24) is known to react with phosphoryl chloride at 0°C to give an anthranilic acid lactam (183), which on heating to 100°C affords the dianthranilate (184)[14]. (Scheme 54).



Scheme 54

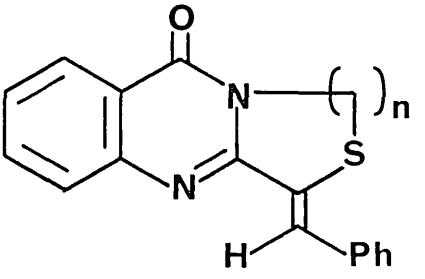
Reactions of Sulphur Containing Quinazolinones with Electrophiles

The reaction of deoxyvasicinone (5), and analagous compounds, with electrophiles at the carbon atom β to the sp^2 hybridised nitrogen atom of the quinazoline ring, has been described by a number of authors (see Introduction). However, as previously noted, the chemistry of the sulphur containing quinazolinones (11)-(13) was largely unknown.

In order to extend our knowledge of these compounds, and compare their reactions with those of deoxyvasicinone (5) type analogues, it was decided to examine the reaction of

(11)-(13) with various electrophiles, at high temperature, and following deprotonation with suitable bases.

Although Daboun[43,44] has reported that the thiazolo [4,3-b] quinazolinedione (96) did not condense with benzaldehyde, the thiazolo[4,3-b]quinazolinone (11) did undergo condensation with benzaldehyde on heating at reflux, to give a phenylmethylene derivative (185). The thiazino analogue (12) also gave a phenylmethylene derivative (186) on heating with benzaldehyde at reflux temperature, whilst the thiazepino compound (13) gave no phenylmethylene derivative, even after prolonged heating with benzaldehyde.



(185) n = 1

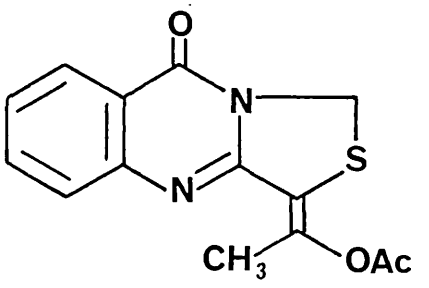
(186) n = 2

However, this was not altogether unexpected, since it has previously been reported that, in general, azepinoquinazolinones are less reactive towards electrophiles compared to their pyrrolo and pyrido counterparts[75].

Like deoxyvasicinone (5), the sulphur containing quinazolinones (11)-(13) did not undergo condensation with aliphatic or unsaturated aldehydes. For example, no

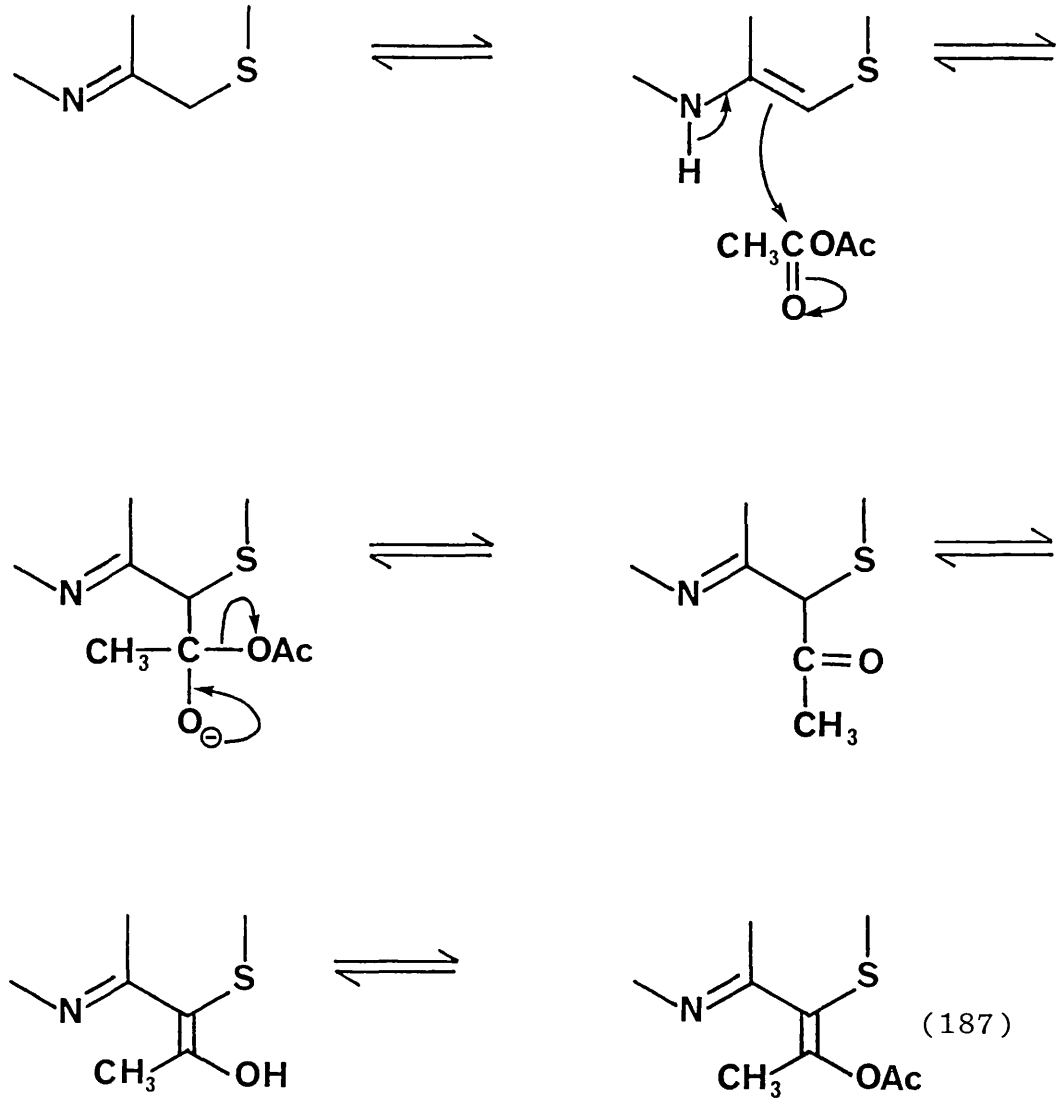
reaction occurred between (11)-(13) and acetaldehyde or cinnamaldehyde.

When the thiazoloquinazolinone (11) was heated at reflux with acetic anhydride, a single enol acetate (187) was obtained in low yield (16%).



(187)

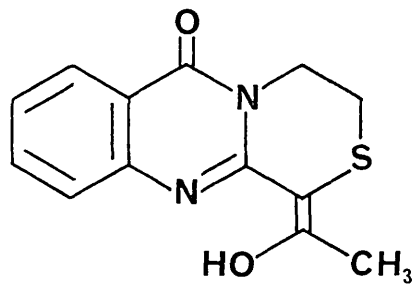
A trace of another compound, presumably a second isomeric enol acetate, was detected (t l.c.) but not isolated. The stereochemistry of the enol acetate (187) could not be definitely assigned by spectroscopic methods. However, it is assumed, by analogy to the major enol acetate isomer produced by the reaction of deoxyvasicinone (5) with acetic anhydride, to have the Z stereochemistry, ie. with the acetoxy group on the opposite side of the double bond to the quinazoline moiety. Formation of the enol acetate (187) may be rationalised by the following reaction mechanism. (Scheme 55).



Scheme 55

Treatment of the thiazinoquinazolinone (12) with acetic anhydride under similar reaction conditions afforded only the hydroxyethylidene derivative (188).

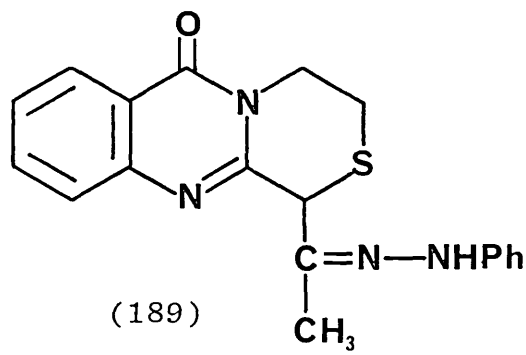
The p.m.r. spectrum of this compound indicated only one isomer, since only one singlet, which integrated for three protons, was apparent for the methyl group.



(188)

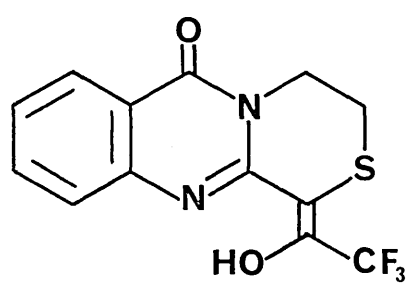
By analogy to the enol obtained on treating the pyridoquinazolinone (22) with acetic anhydride, E stereochemistry is assumed for (188), since this orientation permits stabilisation of the enol by an intramolecular hydrogen bond between the hydroxyl hydrogen and the sp^2 hybridised nitrogen of the quinazoline ring. Both these reactions parallel exactly the behaviour of deoxyvasicinone (5) and the pyridoquinazolinone (22), ie the former yields isomeric enol acetates, whilst the latter gives an enol as the major product. The reason why different products are obtained in these reactions is not as yet understood. Several factors must be considered. Firstly, the steric environment, which may inhibit acetylation of the enol in the case of the six membered C ring compound (12). Secondly, the rate of acetylation of the enol, and reversibility of this reaction. From an examination of Drieding models there does not appear to be any obvious steric hinderance to acetylation of the enol (187) and it therefore appears plausible that the difference is due to the relative stabilities of the enol acetates

produced in the reaction. When the reaction was monitored by t.l.c. no transient intermediate was observed and therefore we believe the acetylation of the enol (188) must be an easily reversed reaction. Although there is no evidence in the p.m.r. or ir spectra of the hydroxyethylidene derivative (188) for the keto tautomer, a phenylhydrazone (189) can be prepared by heating (188) with an ethanolic solution of phenylhydrazine in the presence of glacial acetic acid. Again this mirrors the behaviour of the enol formed on reaction of the pyridoquinazolinone (22) with acetic anhydride.



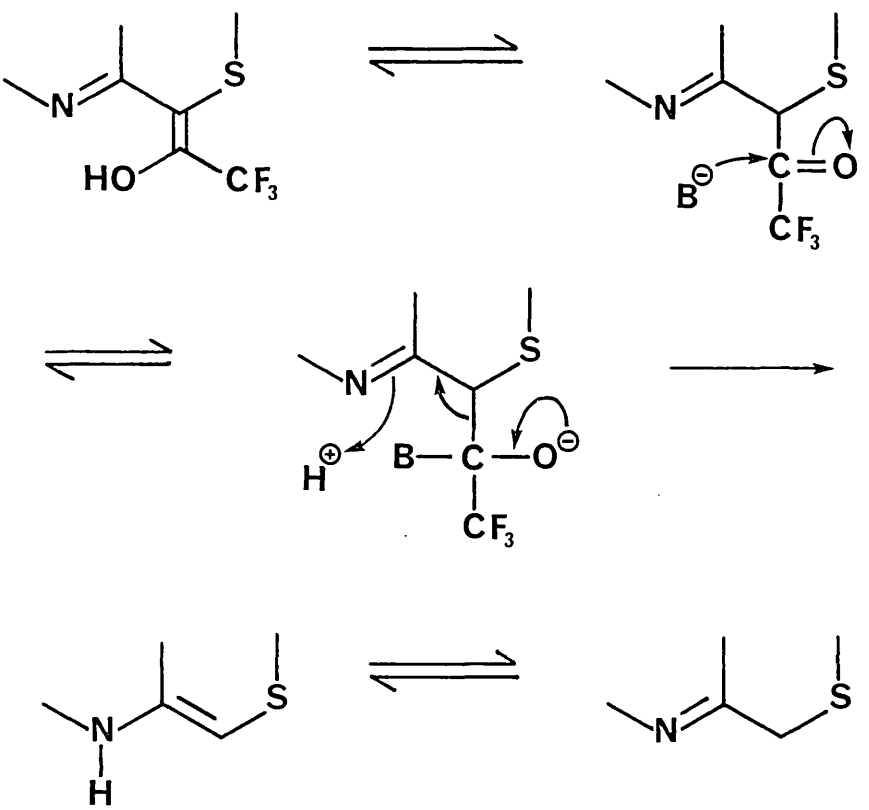
(189)

Rather surprisingly the thiazoloquinazolinone (11) did not undergo reaction with trifluoroacetic anhydride, even after prolonged heating whilst, with the same reagent, the thiazinoquinazolinone (12) yielded the 2,2,2-trifluorohydroxyethylidene derivative (190) in high yield (78%).



(190)

Again there is no evidence (ir, p.m.r.) for the keto tautomer of (190). When this compound was treated with phenylhydrazine/acetic acid in ethanol no phenylhydrazone was obtained, and instead complete deacylation occurred to give (12). The following mechanism is proposed for this process. (Scheme 56).



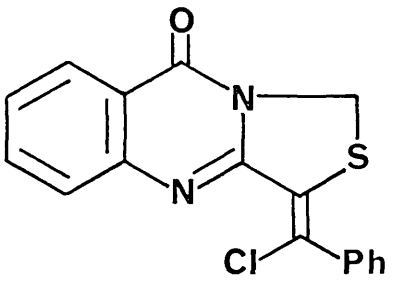
Scheme 56

This type of reaction is not without precedent in fused quinazoline chemistry since it has previously been noted

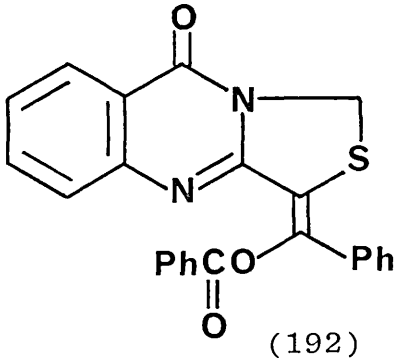
that an ester group at the 3-position of deoxyvasicinone (5) may be removed on treatment with ammonia or its derivatives[35].

It is believed that the failure of the reaction of (11) and trifluoroacetic anhydride is due to the fact that a higher reaction temperature appears to be necessary for reactions involving (11) with electrophiles. Similar behaviour was observed in the reaction of (11) and (12) with thionyl chloride (see later).

When the thiazoloquinazolinone (11) was heated with benzoyl chloride, two compounds were isolated following column chromatography of the reaction mixture. The least polar compound was identified as the α-chlorophenylmethylene derivative (191), whilst the more polar compound was found to be the enol benzoate (192).



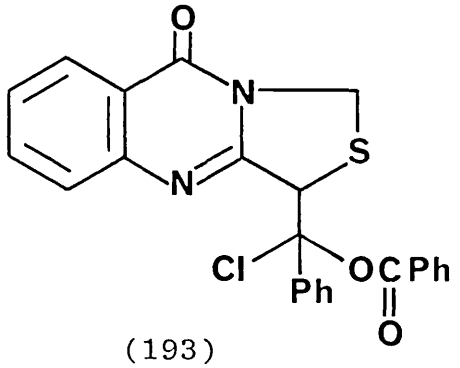
(191)



(192)

Both compounds are assumed, for steric reasons, to have E stereochemistry.

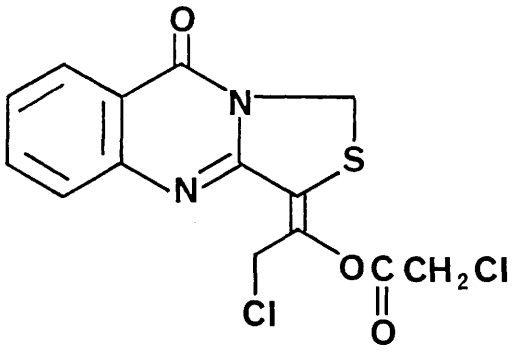
The enol benzoate (192) is formed by a mechanism analogous to that of enol acetate formation (see Scheme 55, p 77). Formation of the α-chlorophenylmethylene derivative (191) almost certainly involves an intermediate of the type (193) which subsequently eliminates benzoic acid.



(193)

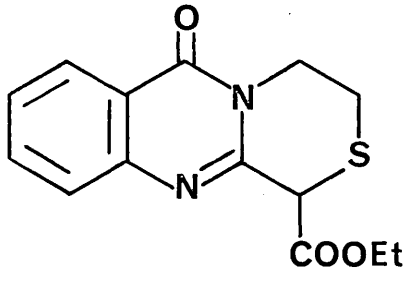
Under the same reaction conditions the thiazinoquinazolinone (12) did not undergo condensation with benzoyl chloride.

The thiazoloquinazolinone (11) did not undergo condensation with acetyl chloride. However, when it was heated with chloroacetyl chloride, a small quantity of an orange solid was obtained, which was identified as (194). The initial product of this reaction was presumably an enol which undergoes reaction with a further mole equivalent of chloroacetyl chloride, in a similar manner to the reactions of (11) with acetic anhydride and benzoyl chloride.



(194)

No reaction could be induced between the thiazoloquinazolinone (11) and ethyl chloroformate, and only extensive decomposition of (11) was observed. When the thiazino analogue (12) was heated at 160°C with the same reagent, the monoester (195) was obtained, albeit in low yield (6%).



(195)

The thiazinoquinazolinone (12) failed to react with chloroacetyl chloride, whilst both (11) and (12) did not undergo condensation when heated with ethyl bromoacetate.

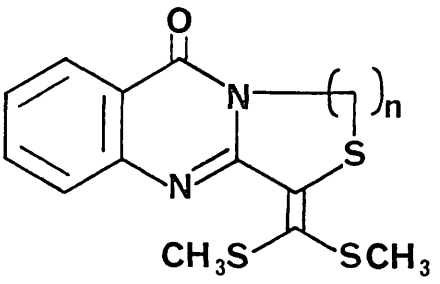
The thiazepinoquinazolinone (13) was found to be inert on heating with acetic anhydride, benzoyl chloride or chloroacetyl chloride. It is believed that the lack of

reactivity of (13) is due to the lower acidity of the protons α to the carbon-nitrogen double bond compared to those of (11) and (12). As a result, the necessary tautomeric shift, which proceeds reaction of these fused quinazolinones with electrophiles, does not readily occur. The major feature of all the reactions of the fused quinazolinones (11)-(13) with electrophiles at high temperature, was the extensive thermal decomposition of these compounds, which resulted in low yields of product.

In view of the problems of thermal decomposition experienced in these reactions, it was decided to investigate the reaction of anions derived from compounds (11)-(13) with electrophiles.

It has previously been shown that fused quinazolinones may be successfully deprotonated using sodium hydride in dry dimethyl sulphoxide, and that the intermediate species may be trapped by the addition of heterocumulenes to the reaction mixture, followed by alkylation[36].

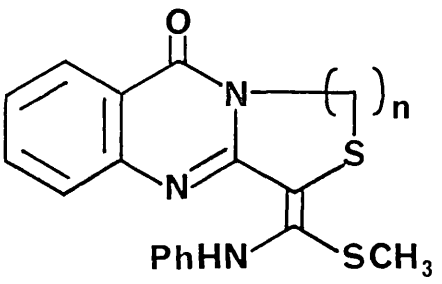
When solutions of the quinazolinones (11)-(13) and carbon disulphide in dry dimethyl sulphoxide were treated with sodium hydride and the intermediates methylated with iodomethane, the ketene S,S-acetals (196)-(198) were obtained. Replacing carbon disulphide by phenyl isothiocyanate in these reactions afforded the ketene S,N-acetals (199)-(201).



(196) n = 1

(197) n = 2

(198) n = 3



(199) n = 1

(200) n = 2

(201) n = 3

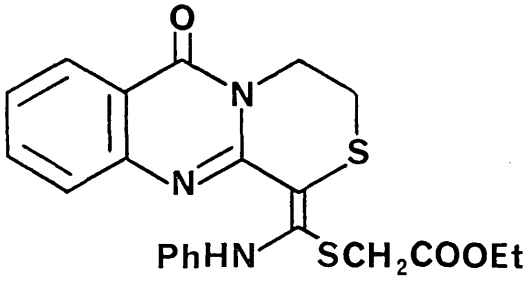
All attempts to displace the methylthio groups in (196) and (197) were unsuccessful. For example, heating these compounds at reflux temperature with excess 1,2-diaminoethane in ethanol afforded only unreacted starting material.

The S,N-acetals (200) and (201) were found to exist as non-separable equilibrium mixtures of stereoisomers. Thin layer chromatography indicated one major and one minor component in each case, and in the p.m.r. spectrum of (200) two signals for the methyl group (ratio 5:1) at δ2.19 and δ2.48 are clearly evident. Unfortunately, complexity in the p.m.r. spectrum of (201) precludes such an analysis, however two signals for the methyl group are again apparent.

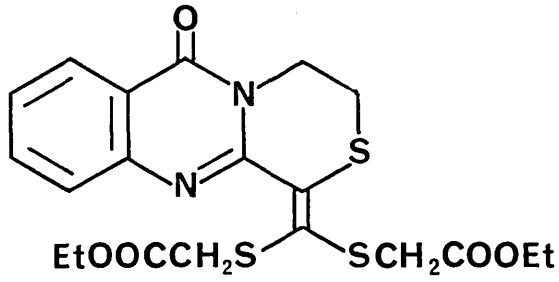
Although low energy barriers to rotation are known to exist in ketene S,N-acetals[76], these will be increased in systems

where the N-H group is involved in intramolecular hydrogen bonding. It is presumed that the strength of these hydrogen bonds is dependent upon the size of the sulphur containing ring, the more rigid the geometry, the stronger the bond and hence the higher the barrier to rotation.

Treatment of the thiazinoquinazolinone (12) with phenyl isothiocyanate/sodium hydride followed by alkylation with ethyl bromoacetate gave the ester (202). Similar treatment of the same compound (12) with carbon disulphide/sodium hydride gave the diester (203) as an unstable red oil.

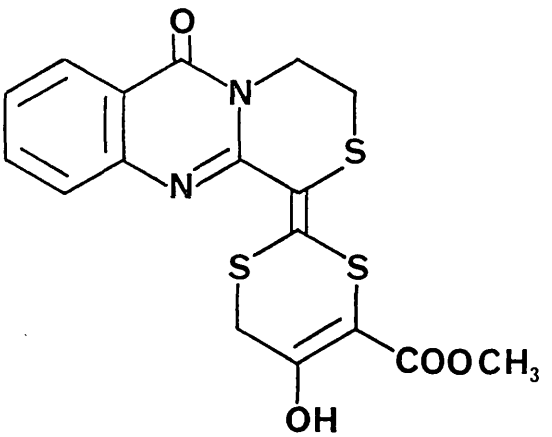


(202)



(203)

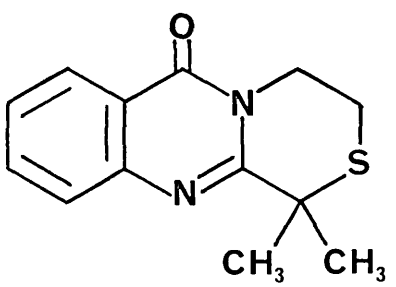
Base (sodium methoxide) induced cyclisation of the crude ester (203), gave the 5,6-dehydro-1,3-dithiane (204) by a Dieckmann type reaction. Transesterification of the presumably initially formed ethyl ester was observed.



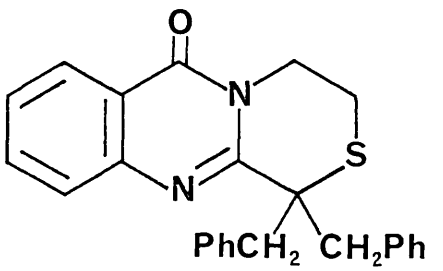
(204)

No new products were isolated when (12) was treated with ethoxycarbonyl isothiocyanate and sodium hydride in dry dimethyl sulphoxide. The success of the majority of these reactions prompted an investigation into the base catalysed reaction of the thiazinoquinazolinone (12) with other electrophiles and with Michael acceptors.

Thus, when (12) was treated with excess sodium hydride and iodomethane in dry DMF, the dimethyl compound (205) was obtained. Similar treatment of (12) using benzyl bromide as the alkylating agent gave the dibenzyl derivative (206).



(205)



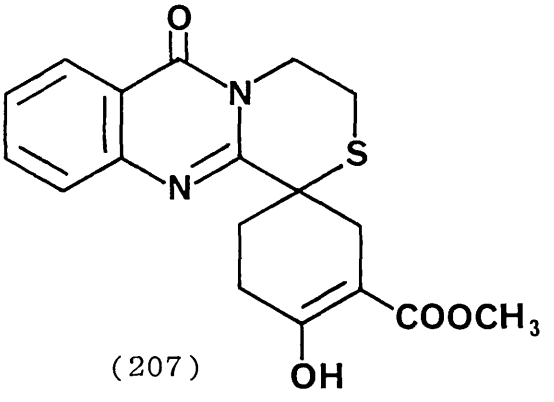
(206)

However, when ethyl bromoacetate was employed as the electrophile, no reaction was evident and only unreacted (12) was isolated.

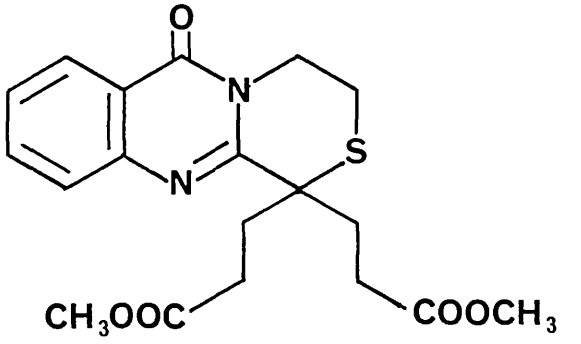
It is believed that the failure of this reaction to yield any new products is as a result of rapid proton exchange between the quinazolinone anion (a very powerful base) and the relatively more acidic α-protons of the ethyl bromoacetate. Similarly no reaction took place when (12) was treated with sodium hydride and the reaction quenched with acetyl chloride. However rather surprisingly no reaction was observed when a solution of the anion of (12) was treated with either benzoyl chloride or ethyl chloroformate. Since these latter electrophiles do not possess α-hydrogens no logical reason for the failure of these reactions can be forwarded.

In the presence of sodium hydride and in dry DMF solution the quinazolinone (12) underwent Michael addition reactions.

Thus when (12) was stirred with sodium hydride in the presence of methyl acrylate, the spiro compound (207) was isolated. The compound (207) is formed by base catalysed Dieckmann ring closure of the transient intermediate diester (208).

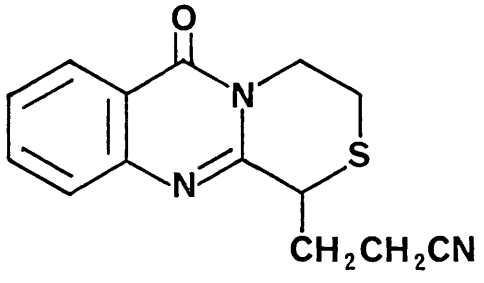


(207)



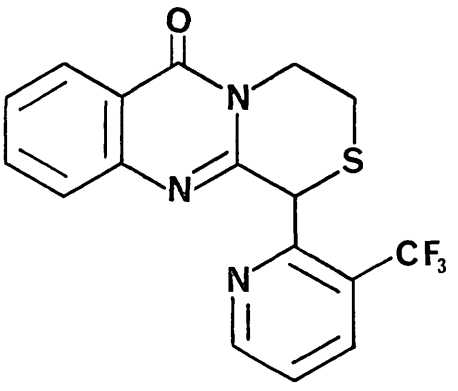
(208)

Under similar conditions using acrylonitrile as the Michael acceptor the sole reaction product was the monocyanoethyl derivative (209). Reaction of (12) with methyl methacrylate/sodium hydride resulted in a complex mixture, the components of which could not be resolved. Attempted addition of methyl vinyl ketone failed and only unreacted (12) was recovered.



(209)

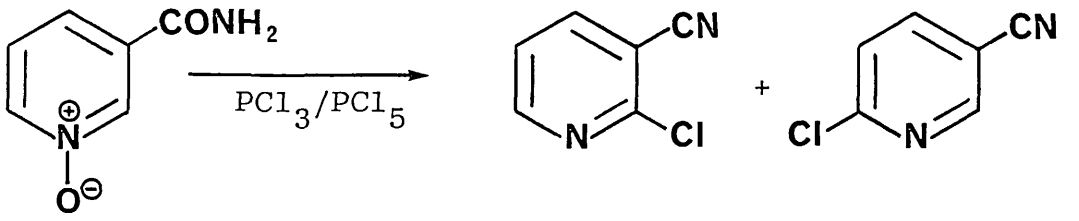
It is well known that halogen atoms in the 2(6) and 4 positions of pyridine rings can be easily replaced by nucleophiles, especially when electron withdrawing groups are present ortho and para to the halogen atom[77]. When a mixture of (12) and 2-chloro-3-trifluoromethylpyridine in dry DMF was stirred with sodium hydride, nucleophilic displacement of the chlorine occurred and compound (210) was obtained.



(210)

The success of this reaction prompted a further investigation into the reaction of (12) with activated halopyridines, in particular chlorocyanopyridines, in the presence of sodium hydride. The chlorocyanopyridines required for this study were 2-chloro-3-cyanopyridine (212), 4-chloro-3-cyanopyridine (215) and 3-chloro-2-cyanopyridine (217). All three were prepared by literature methods or slight modifications thereof. Treatment of nicotinamide-N-oxide (211) with a mixture of phosphorus trichloride and phosphorus pentachloride, according to the method of Taylor et al[78], gave 2-chloro-3-cyanopyridine (213) in 35% yield. Chromatography of the reaction residues afforded,

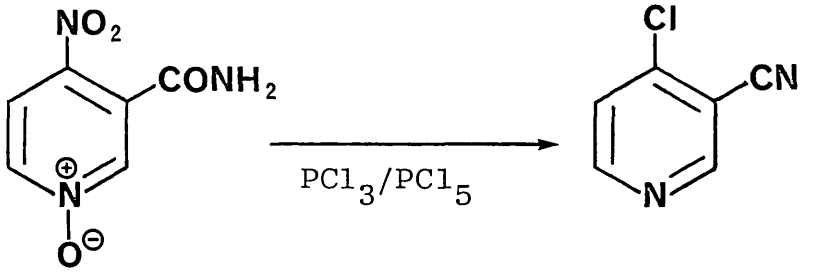
in addition to further (213), 2-chloro-5-cyanopyridine (212) as a minor product. (Scheme 57).



(211) (212) (213)

Scheme 57

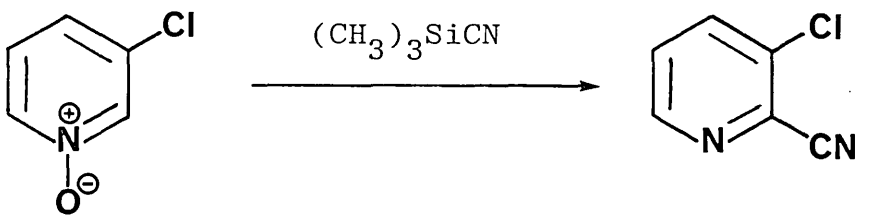
4-Chloro-2-cyanopyridine (215) was prepared in 40% yield by treating 4-nitronicotinamide-N-oxide (214) with phosphorus trichloride and phosphorus pentachloride[79] (Scheme 58).



(214) (215)

Scheme 58

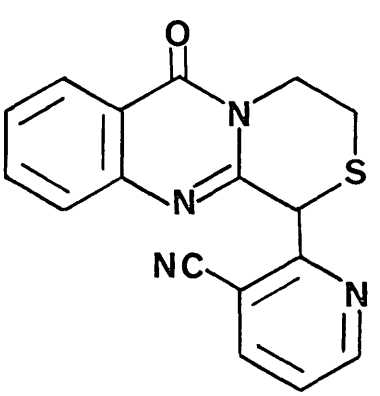
3-Chloro-2-cyanopyridine (217) was obtained on stirring a dichloromethane solution of 3-chloropyridine-N-oxide (216), trimethylsilylcyanide and dimethylcarbamoyl chloride for seven days[80]. (Scheme 59).



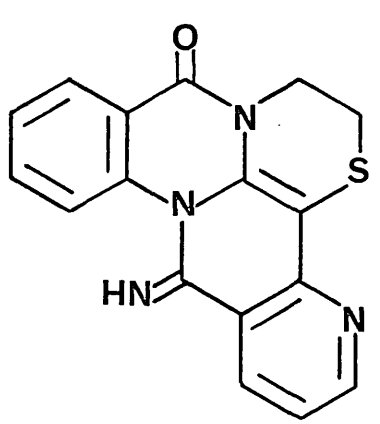
(216) (217)

Scheme 59

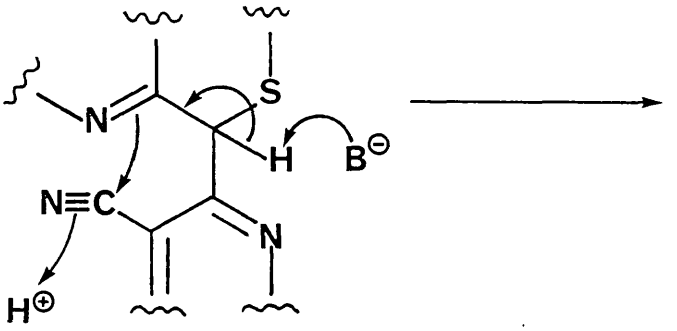
When a solution of the thiazinoquinazolinone (12) and 2-chloro-3-cyanopyridine (212) was stirred with sodium hydride, two products were detected by t.l.c.. These were separated by column chromatography. The minor product (218) resulted from expected nucleophilic attack of the anion of (12) on the chlorocyanopyridine (212), with resultant replacement of the chlorine atom by the thiazinoquinazolinone group. The major product was shown to have the structure (219) on consideration of its analytical and spectral data. The formation of (219) may be rationalised on the basis of the following reaction mechanism. (Scheme 60).



(218)



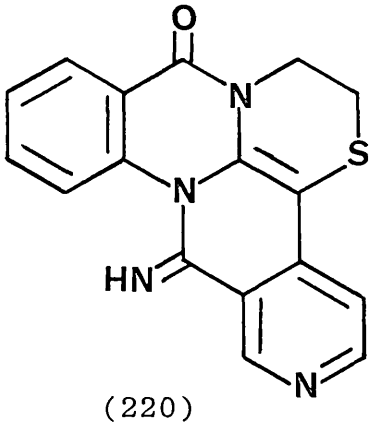
(219)



(219)

Scheme 60

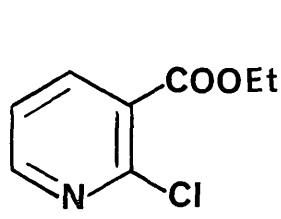
When a mixture of the thiazinoquinazolinone (12) and 4-chloro-3-cyanopyridine (215) was treated with excess sodium hydride, a single product was isolated which was identified by spectroscopy and elemental analysis as (220).



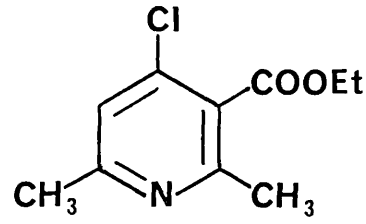
(220)

No arylation was observed when (12) was treated with 3-chloro-2-cyanopyridine (217) in the presence of excess sodium hydride. Ortho halogenated pyridine esters, for example, ethyl 2-chloropyridine-3-carboxylate (221) and

ethyl 4-chloropyridine-3-carboxylate (222) failed to react with (12) in the presence of sodium hydride.



(221)



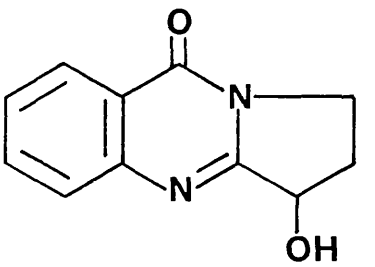
(222)

Other studies in this laboratory have shown that the halogen atoms in these molecules are less readily replaced by nucleophiles[81].

Oxidation and Pummerer Rearrangement

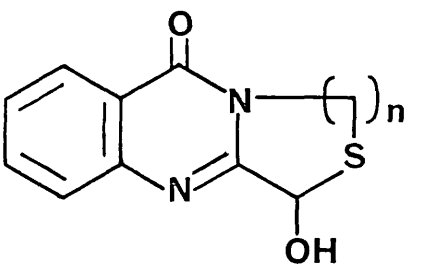
Despite the numerous studies undertaken in an effort to establish structure/activity relationships in fused quinazoline alkaloids, no definitive rules have been established. However, a comprehensive investigation by Sharma et al[82] has shown that, in general, bronchiodilatory activity may be enhanced by the presence of an oxygen atom at C-3 or C-9 of the pyrroloquinazoline molecule. If either the carbonyl group in deoxyvasicinone type derivatives, or the hydroxyl group in vasicine type analogues are absent, then a subsequent reduction in the biological activity of the molecule is observed. For example, vasicinone (223) is considerably more biologically active than either

vasicine (4) or deoxyvasicinone (5).



(223)

It was therefore decided to attempt the preparation of the sulphur containing derivatives of vasicinone (224) and also the higher analogues (225) and (226).



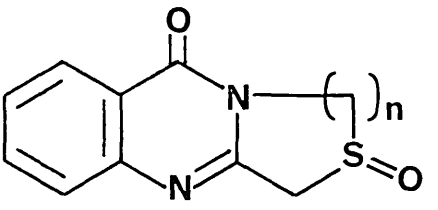
(224) n = 1

(225) n = 2

(226) n = 3

It was anticipated that these compounds could be prepared from sulphoxides derived from the quinazolinones (11)-(13), by a Pummerer type rearrangement. When the quinazolinones (11)-(13) were treated with 3-chloroperoxybenzoic acid in cold dichloromethane, the required sulphoxides (227)-(229) resulted. The p.m.r. spectra of these sulphoxides (227)-(229) showed increased complexity when compared to the

parent quinazolinones.



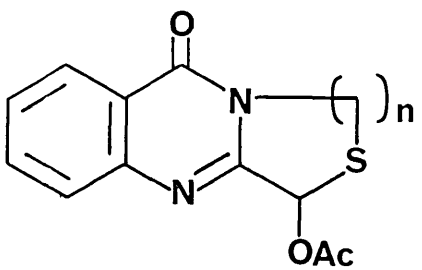
(227) n = 1

(228) n = 2

(229) n = 3

The methylene protons at C-1 of the thiazolo sulphoxide (227) became anisochronous, the original singlet at δ5.08 in (11) being replaced by two doublets (J 13.7Hz) at δ4.95 and δ5.40. Since the protons at C-3 are not similarly effected it seems likely that the non-equivalence at C-1 results as a consequence of interactions between these protons and both the sulphoxide function and the lone pair on the amidic nitrogen atom. Extreme complexity of all C ring protons occurred in the case of the thiazino and thiazepino sulphoxides, (228) and (229), which prevented detailed analysis of the spectra. This complexity was due to the extensive vicinal and geminal coupling throughout the spectrum as a result of the non-equivalence of the protons in the thiazino and thiazepino rings. All three sulphoxides exhibited a characteristic, strong S-O str. band in the ir spectrum. The sulphoxides (227)-(229)

readily underwent facile Pummerer rearrangement when heated for a short period with acetic anhydride to give the acetoxy derivatives (230)-(232).

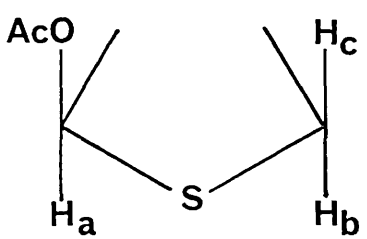


(230) n = 1

(231) n = 2

(232) n = 3

The protons at C-1 of the thiazolo acetoxy derivative (230), like those of the sulphoxide (227), appeared as a pair of doublets. In addition, long range W coupling was also evident. (Scheme 61).

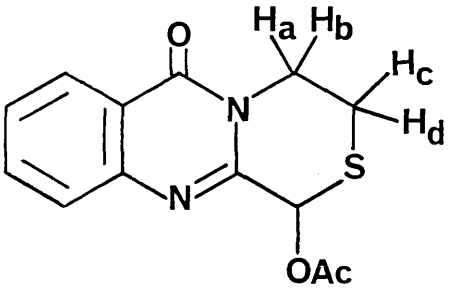


J_{AB} = 0.8Hz

Scheme 61

The protons adjacent to the amidic nitrogen in the acetoxy derivatives (231) and (232) are clearly anisochronous,

however, only in the case of the thiazino compound (231) could the coupling constants be examined in greater detail.



(231)

Ha and Hb are geminally coupled (J 14Hz) and each is vicinally coupled to Hc and Hd.

Jac	3Hz	Jbc	4.5Hz
Jab	4Hz	Jbd	12 Hz

Although many variables are important in deciding the magnitude of the vicinal coupling constant (Jvic), the factor which is most easily predicted in its influence on Jvic, is the dihedral angle Ø between the two vicinal C-H bonds. The influence of the dihedral angle Ø on Jvic is easily predicted using the Karplus equations, the values obtained frequently being reasonably close to observed values.

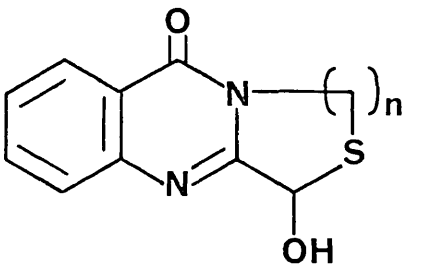
Karplus Equations

Ø between 0° and 90° : $J_{vic} = 8.5 \cos^2\emptyset - 0.28$

Ø between 90° and 180° : $J_{vic} = 9.5 \cos^2\emptyset - 0.28$

It is more convenient to express this graphically, and indeed the reliability of the method is not sufficiently high to justify accurate calculations.

In compound (231) the smaller coupling constants (3-4.5 Hz) are consistent with predicted dihedral angles of approximately 60°, whilst the larger coupling constant (12 Hz) is consistent with the value normally associated with protons separated by a dihedral angle of 180°. From an examination of Drieding models and from a consideration of the above data, it appears that the reduced thiazine ring (the C ring) exists in a boat or a half-chair conformation and that an energy barrier to ring flip exists. In these conformations only one of the protons on the carbon atom adjacent to the amidic nitrogen atom (C-4) experiences a deshielding effect due to the ring carbonyl. Deacetylation of the acetoxy derivatives (230)-(232) with sodium methoxide (Zemplen) gave the alkanols (233)-(235).

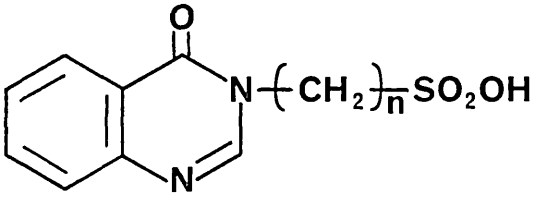


(233) n = 1

(234) n = 2

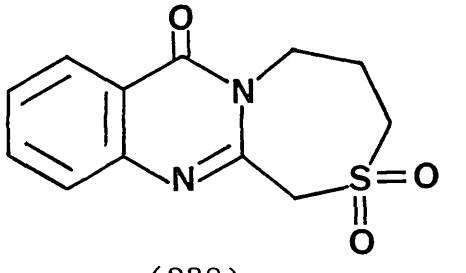
(235) n = 3

Under more vigorous oxidising conditions, using a mixture of hydrogen peroxide and glacial acetic acid, the thiazolo and thiazino quinazolinones (11) and (12) underwent oxidative ring opening to yield the sulphonic acids (236) and (237) respectively. It has previously been reported that thiazolidines give disulphides or sulphonic acids on treatment with oxidising agents (I_2, Br_2, H_2O_2)[83]. Similar treatment of the thiazepino derivative (13) did yield a sulphone (238).



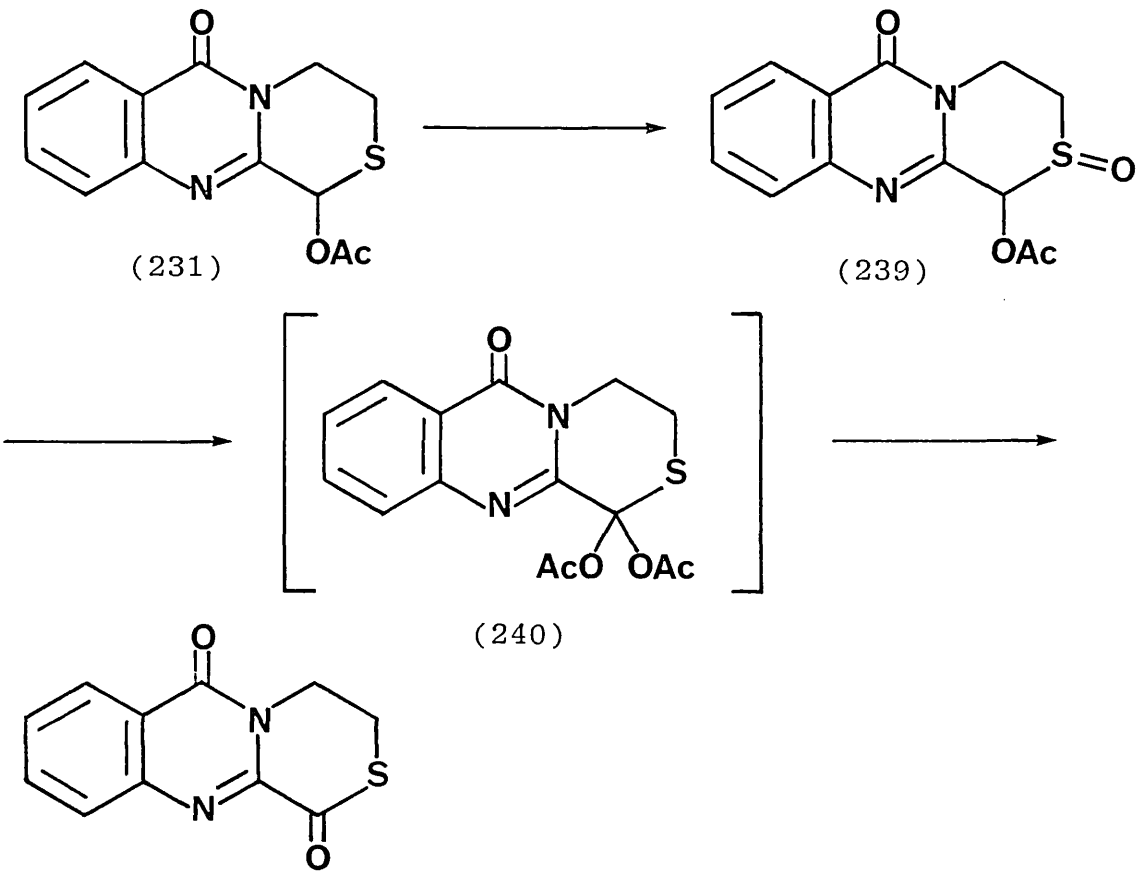
(236) n = 1

(237) n = 2



(238)

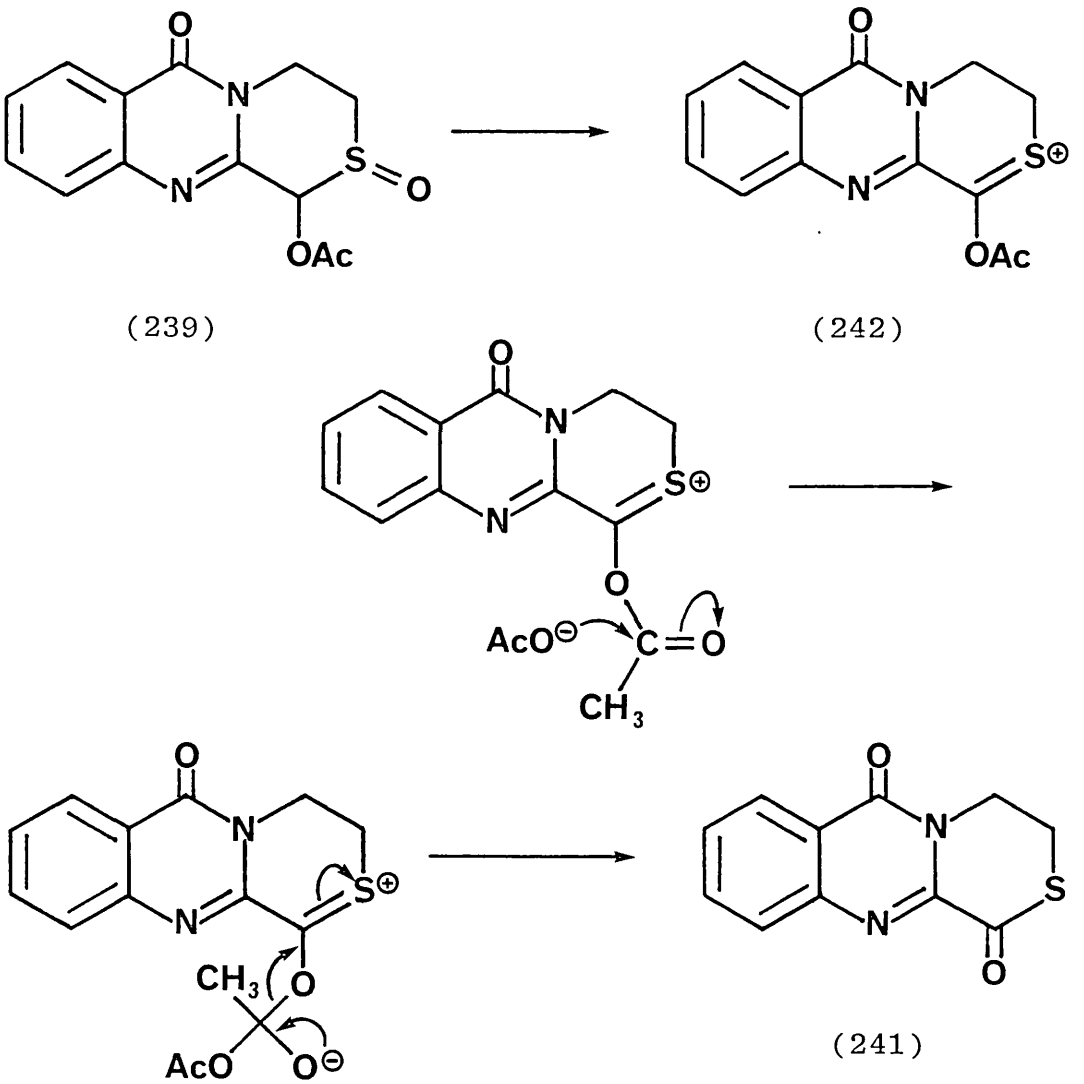
Although the oxidation of deoxyvasicinone (5) at the 3-position to give the 3-oxo derivative has never been achieved, in this study the thiazinoquinazolinone (12) was oxidised to give the equivalent 1-oxo compound. Reoxidation of the acetoxy compound (231) with 3-chloroperoxybenzoic acid gave the sulphoxide (239), which on heating in acetic anhydride gave the 1-oxo derivative (241). The reaction may proceed by normal Pummerer rearrangement of the sulphoxide (239) followed by elimination of acetic anhydride from a transient gem diacetoxy derivative (240). (Scheme 62).



(231) (239) (240) (241)

Scheme 62

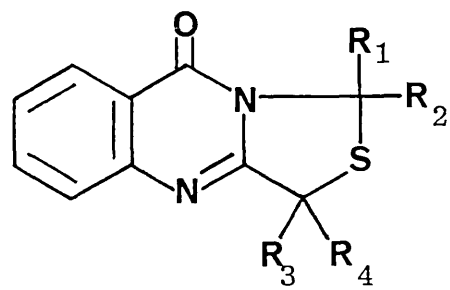
However it is equally possible that (241) may be formed by attack of acetate on the acetoxy carbonyl carbon of the resonance stabilised sulphenium ion (242), followed by elimination of acetic anhydride. (Scheme 63).



Scheme 63

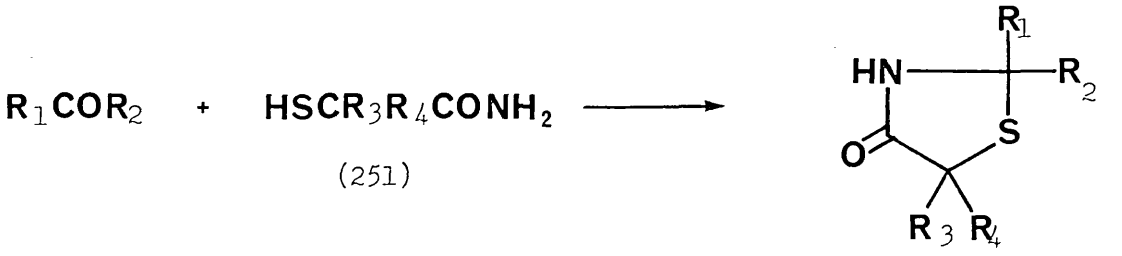
The relative ease of Pummerer rearrangement of the sulphoxide (227) prompted an investigation into the reaction of substituted thiazolidine ring analogues of the sulphoxide (227) under similar reaction conditions. It was therefore

decided to prepare a series of methyl substituted analogues of (11), ie (243)-(250), and examine the effect of hot acetic anhydride on their sulphoxides. As before the quinazolinones (243)-(247) were conveniently prepared by the condensation of the appropriate substituted 4-thiazolidinones with anthranilic acid using the method of Shakhidoyatov[14].



	R_1	R_2	R_3	R_4
(243)	CH_3	H	H	H
(244)	CH_3	CH_3	H	H
(245)	CH_3	CH_3	CH_3	H
(246)	CH_3	CH_3	CH_3	CH_3
(247)	CH_3	H	CH_3	H
(248)	H	CH_3	CH_3	CH_3
(249)	H	H	CH_3	CH_3
(250)	H	H	H	CH_3

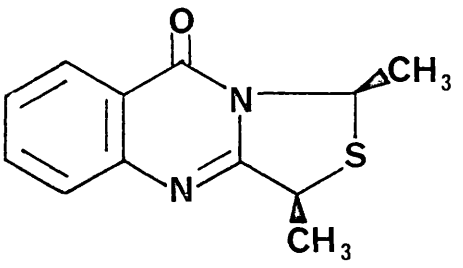
The required substituted 4-thiazolidinones (252)-(256) were prepared by the acid catalysed condensation of the appropriate mercaptoamide (251) with acetaldehyde or acetone. (Scheme 64).



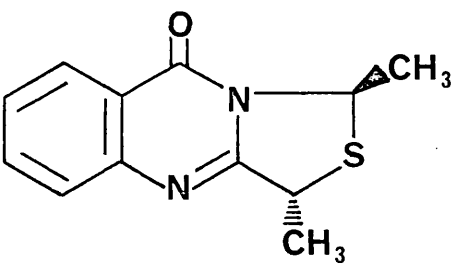
	R_1	R_2	R_3	R_4
(252)	CH_3	H	H	H
(253)	CH_3	CH_3	H	H
(254)	CH_3	CH_3	CH_3	H
(255)	CH_3	CH_3	CH_3	CH_3
(256)	CH_3	H	CH_3	H

Scheme 64

Thus heating the 4-thiazolidinones (252)-(255) with anthranilic acid (24) in the presence of phosphoryl chloride gave the quinazolinones (243)-(246) in good yield. When (256) was treated similarly a two component mixture was obtained which was resolved by column chromatography. The resulting compounds were assigned the structures (247a) and (247b) after consideration of spectroscopic and elemental data.



(247a)



(247b)

Both these compounds (247a) and (247b) analysed as $C_{12}H_{12}N_2OS$ and had practically identical m.p., ir, m.s. and p.m.r. but were clearly distinguishable on t.l.c..

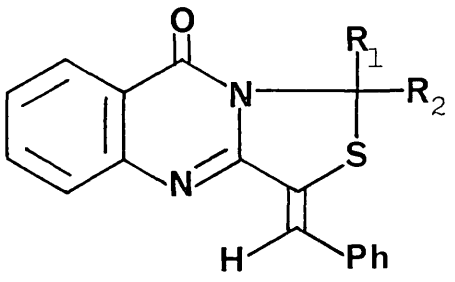
The 4-thiazolidinones required for the synthesis of the thiazoloquinazolinones (248)-(250) could not be produced in sufficient quantities for condensation, since the mercaptoamide (251 $R_3 = R_4 = CH_3$) was extremely difficult, costly and time consuming to produce. However, all three compounds could be prepared by C-methylation of (243) and (11).

When the quinazolinones (243) and (11) were treated with 2.5 mole equivalents of sodium hydride, in the presence of 2.5 mole equivalents of iodomethane in dry DMF, the compounds (248) and (249) resulted respectively.

When (11) was treated with 1.1 mole equivalents of sodium hydride in the presence of 1.1 mole equivalents of

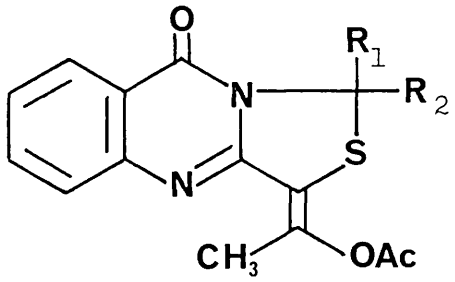
iodomethane in dry DMF, a three component mixture was obtained. The mixture was resolved by column chromatography to give the desired monomethyl quinazolinone (250) as the major product (32%). Further elution gave the dimethyl compound (249) and unreacted (11), both identical (m.p., ir, p.m.r.) to authentic samples, in 20 and 22% yield respectively.

The compounds (243) and (244) showed similar reactivity to the unsubstituted quinazolinone (11). Both these compounds underwent condensation with benzaldehyde to give phenylmethylene derivatives (257) and (258), and with acetic anhydride to afford enol acetates (259) and (260).



(257) $R_1 = CH_3$, $R_2 = H$

(258) $R_1 = R_2 = CH_3$



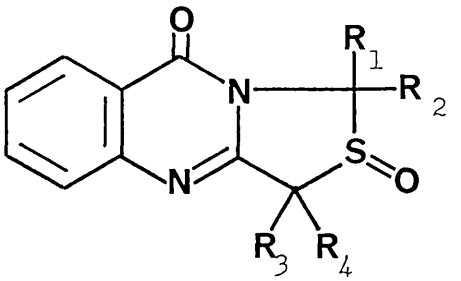
(259) $R_1 = CH_3$, $R_2 = H$

(260) $R_1 = R_2 = CH_3$

However, no condensation occurred between benzaldehyde or acetic anhydride and quinazolinones possessing a substituent at the active methylene group (C-3).

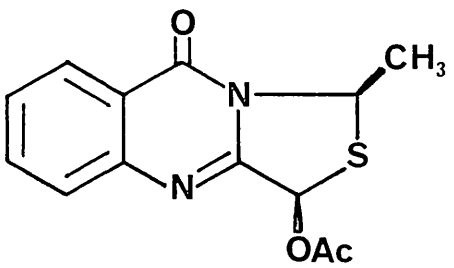
Oxidation of the quinazolinones (243)-(250) with 3-chloroperoxybenzoic acid in dichloromethane gave the

corresponding sulphoxides (261)-(268).

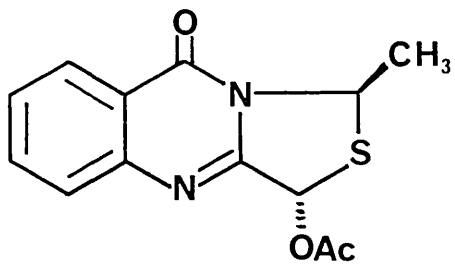


	R_1	R_2	R_3	R_4
(261)	CH_3	H	H	H
(262)	CH_3	CH_3	H	H
(263)	CH_3	CH_3	CH_3	H
(264)	CH_3	CH_3	CH_3	CH_3
(265)	CH_3	H	CH_3	H
(266)	H	CH_3	CH_3	CH_3
(267)	H	H	CH_3	CH_3
(268)	H	H	H	CH_3

When the sulphoxide (261) was heated with acetic anhydride, two isomeric acetoxy derivatives (269a) and (269b) of almost identical Rf were obtained. These were separable by careful column chromatography. All spectroscopic data recorded



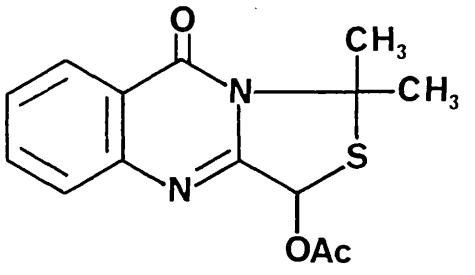
(269a)



(269b)

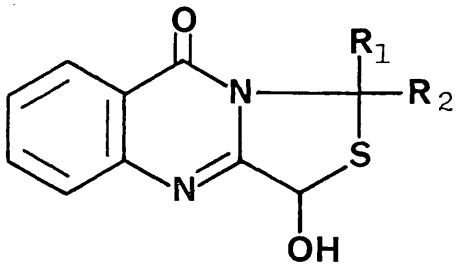
on these two isomeric acetates was virtually the same, although a difference in melting point of 40°C confirmed the two compounds were not structurally identical.

Heating the sulphoxide (262) with acetic anhydride gave the acetoxy compound (270) as a green glassy solid following short path bulb to bulb distillation (Kugelrohr) of the crude reaction product.



(270)

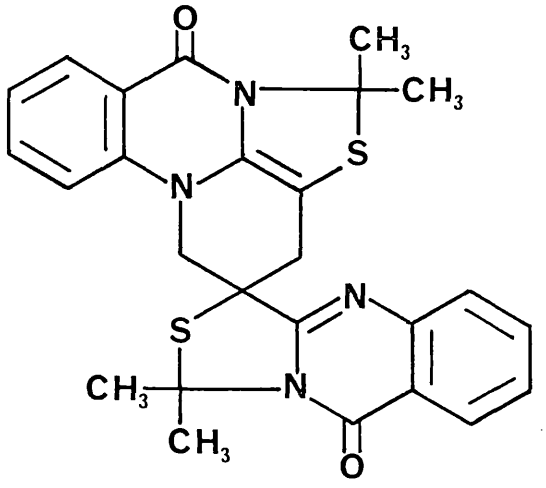
Deacetylation of the acetoxy derivatives (269a) and (270) by the method of Zemplen afforded the corresponding hydroxy derivatives (271) and (272).



(271) $R_1 = CH_3$, $R_2 = H$

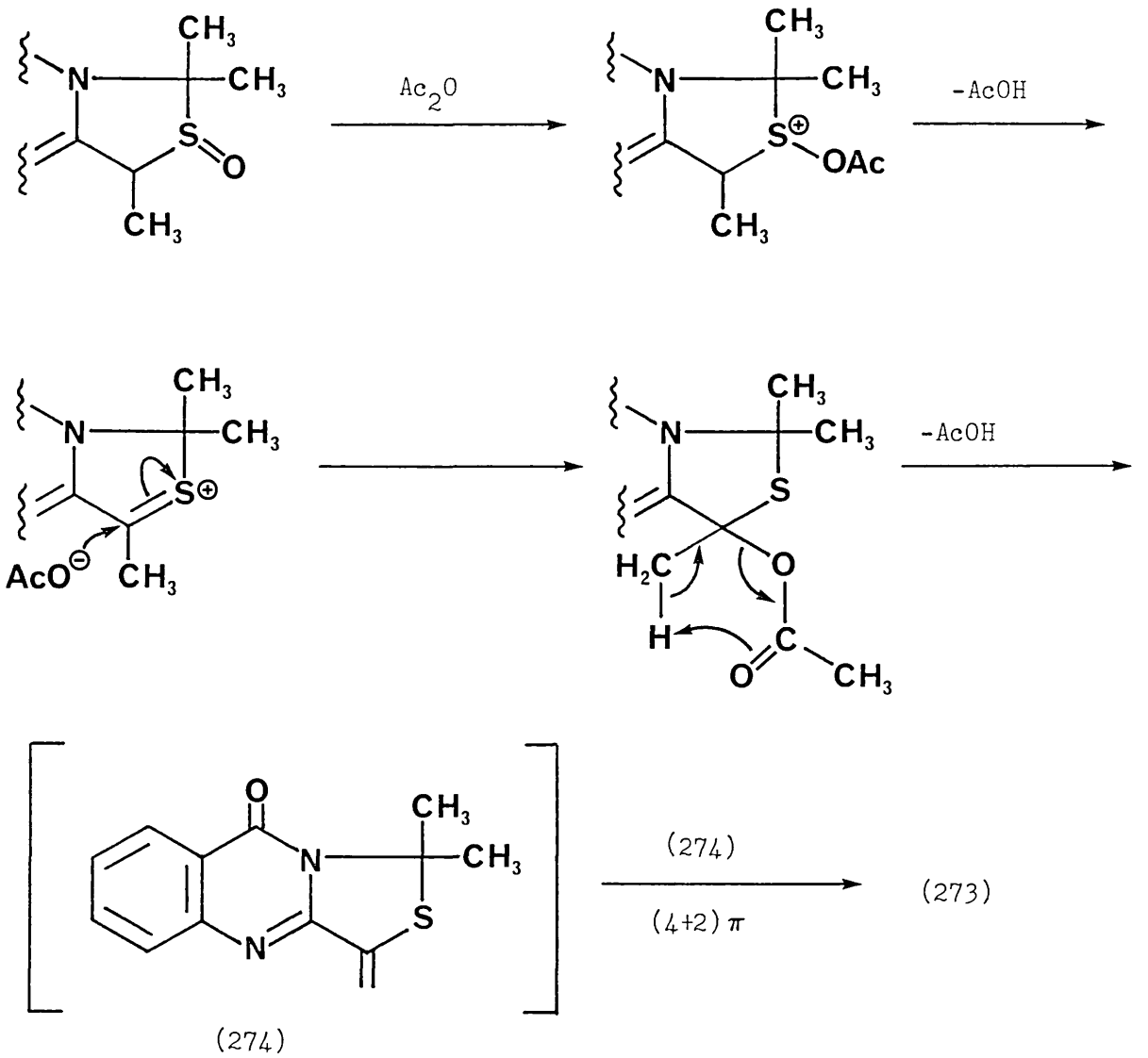
(272) $R_1 = R_2 = CH_3$

When the sulphoxide (263) was heated with acetic anhydride a small amount of a yellow crystalline solid was obtained. Infrared spectroscopy revealed that the solid did not contain an acetoxy group and both elemental analysis and mass spectrometry indicated the formula $C_{26}H_{24}N_4O_2S_2$. These facts and the p.m.r. spectrum of the compound suggest structure (273).



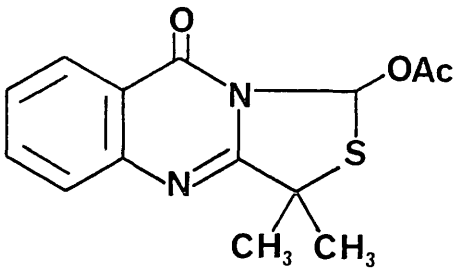
(273)

Further evidence for the structure (273) was provided by mass spectrometry measurements. The presence of a molecular ion at $^{m}/e$ 488, and a fragment $^{m}/e$ 244, indicative of a retro Diels-Alder fragmentation, suggests that the compound assigned structure (273) is produced by a Diels-Alder cycloaddition of two molecules of the exomethylene derivative (274), which may be generated as shown in Scheme 65 .



Scheme 65

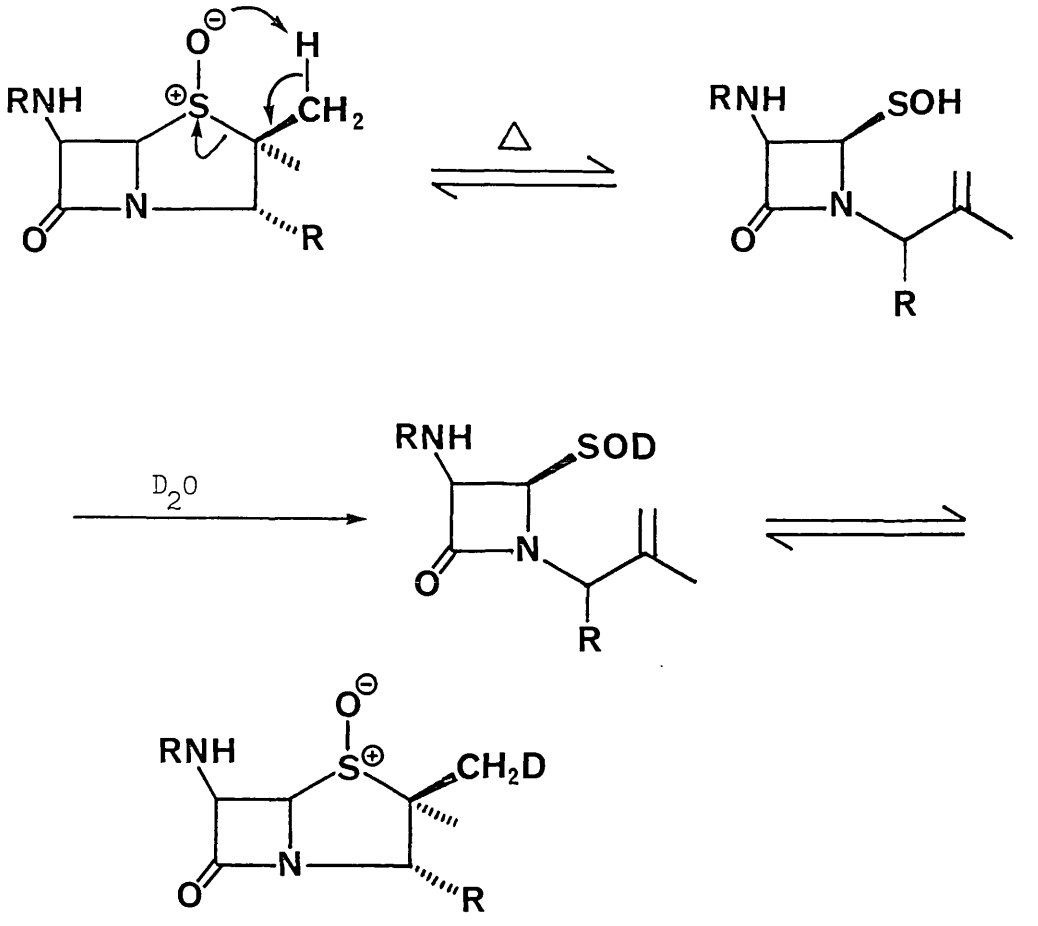
Heating the sulphoxides (264), (265), (266) and (268) with acetic anhydride afforded no new products. However, similar treatment of sulphoxide (267) resulted in a relatively slow Pummerer rearrangement which afforded the acetoxy derivative (275).



(275)

Although Pummerer rearrangement did occur in this instance, the reaction proceeds approximately twenty times more slowly than in those compounds which were unsubstituted at the 3-position, for example (11). The rate determining step of the rearrangement, ie formation of the ylide (see Scheme 44, p 61), is slower due to the relative lack of acidity of the protons at the 1-position, compared to those at the 3-position.

For a number of years[84] it has been known that, on pyrolysis, some sulphoxides can undergo a retro-ene type reaction, analagous to the Cope elimination of amine oxides, which is of considerable mechanistic interest and synthetic utility. The reaction involves a five-membered, six electron transition state (four electrons from the C-S and C-H σ bonds, two electrons from the sulphoxide oxygen) and is reversible. This reversibility is excellently demonstrated with penicillin sulphoxides, by deuterium exchange studies and by actual isolation of the penicillin sulphenic acid[85] (Scheme 66).

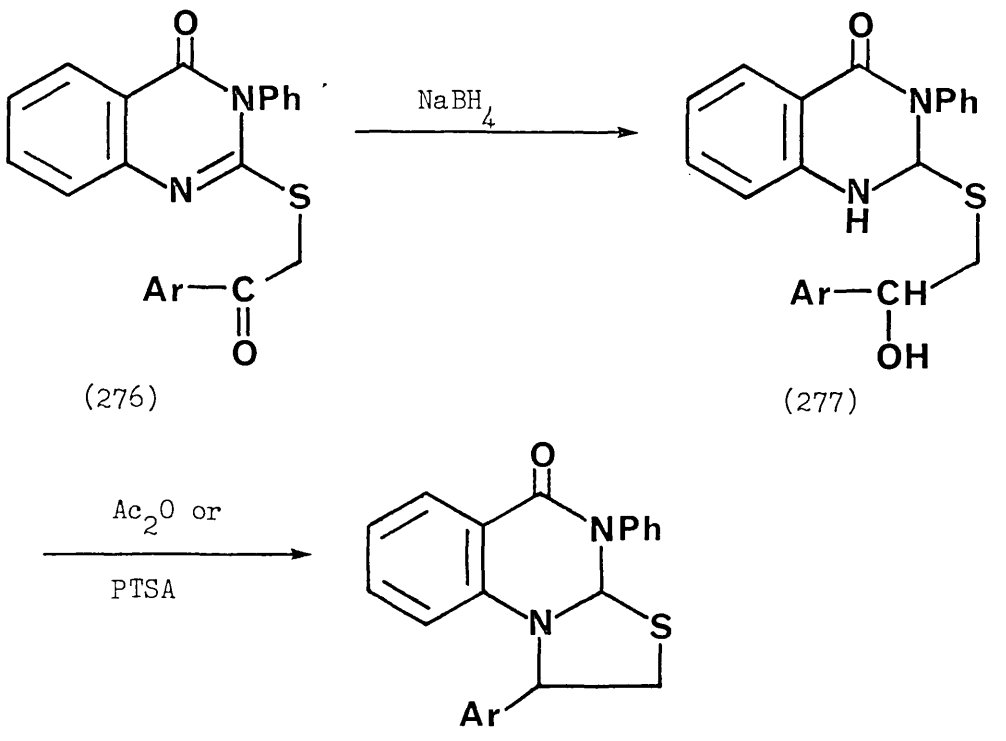


Scheme 66

However, all attempts at generating and trapping sulphenic acids from thiazoloquinazolinone sulphoxides prepared in this study proved unsuccessful. No new products were obtained on heating sulphoxide (264) with acetic anhydride, dimethyl acetylenedicarboxylate or N-chlorosuccinimide. Furthermore, examination (by p.m.r.) of the product obtained by heating (264) under reflux with a trace of deuterium oxide in benzene, showed no deuterium had been incorporated into the molecule. Thus there is no evidence for the generation of sulphenic acids from these quinazolinone sulphoxides under the mild conditions employed in this study.

Reduction

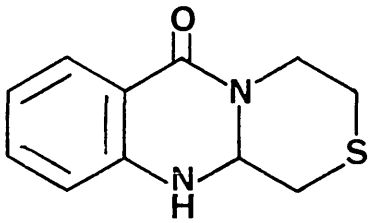
The use of sodium borohydride to effect the reduction of aldehydes and ketones is a well-established and widely utilised procedure. In addition, sodium borohydride has also been shown to be effective in the reduction of the imine double bond of certain nitrogen heterocycles[86,87] For example, substituted thiazolo[3,2-a]quinazolinones of the type (278) were prepared in good yield by reduction of (276) with sodium borohydride, followed by cyclodehydration of the intermediate alkanol (277) with acetic anhydride or para-toluene sulphonic acid[88]. (Scheme 67).



(276) (277) (278)

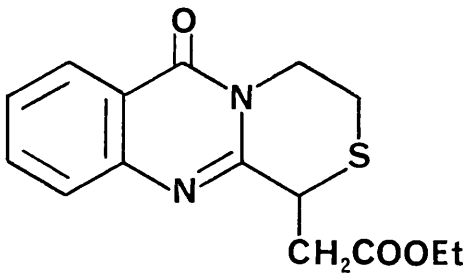
Scheme 67

Initial investigations into the reduction of the thiazinoquinazolinone (12) showed that the dihydroquinazolinone (279) was conveniently prepared on treating the former with sodium borohydride in ethanol or acetic acid[89].



(279)

It was envisaged that the reduction of a suitably substituted analogue of (12) could lead to novel tetracyclic compounds. A compound which was deemed to possess the necessary structural and steric features for such a reductive cyclisation was the ester (280).



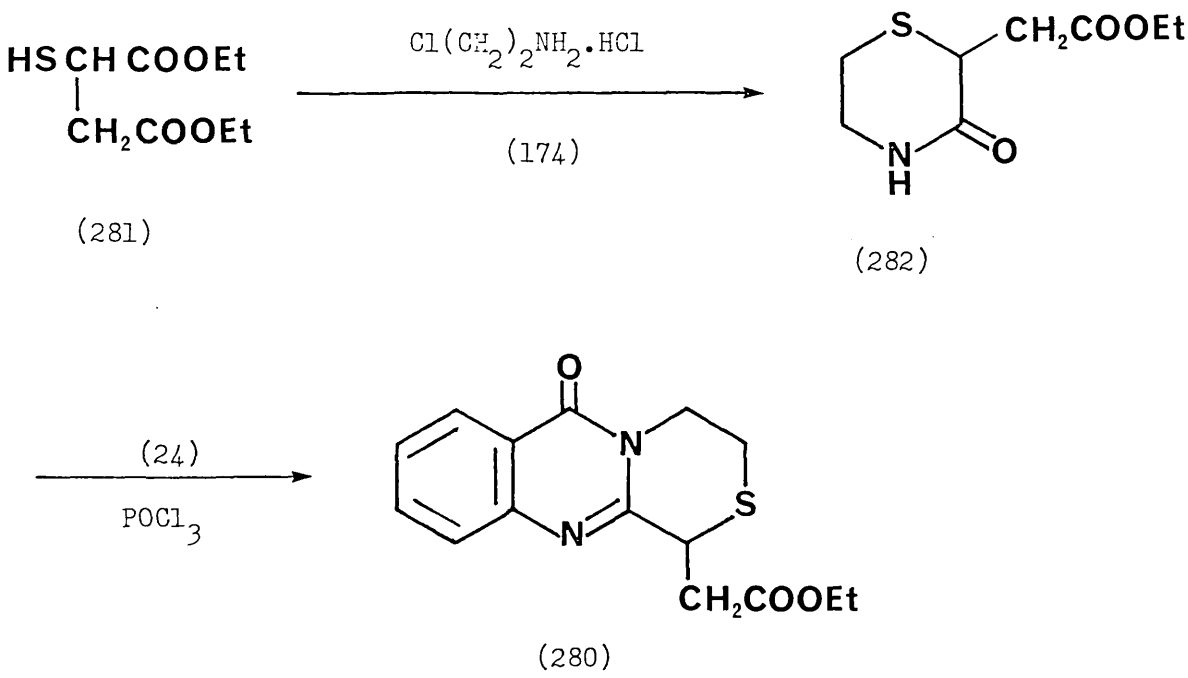
(280)

Previous attempts at synthesising the ester (280) during the course of this study had proved unsuccessful. Direct condensation between the quinazolinone (12) and ethyl bromoacetate at high temperature, or with ethyl

bromoacetate in the presence of base, failed to realise any of the required ester (280) (see p 83 and p 88). In view of this, it was therefore decided to attempt the preparation of (280) using the method of Shakhidoyatov[14].

The required substituted 3-oxothiomorpholine (282) was prepared by the base (sodium methoxide) catalysed condensation of ethyl mercaptosuccinate (281) with 2-chloroethylamine hydrochloride (174). Although theoretically a mixture of six and seven membered lactam was possible, it was anticipated that the thermodynamically more stable six membered compound would predominate.

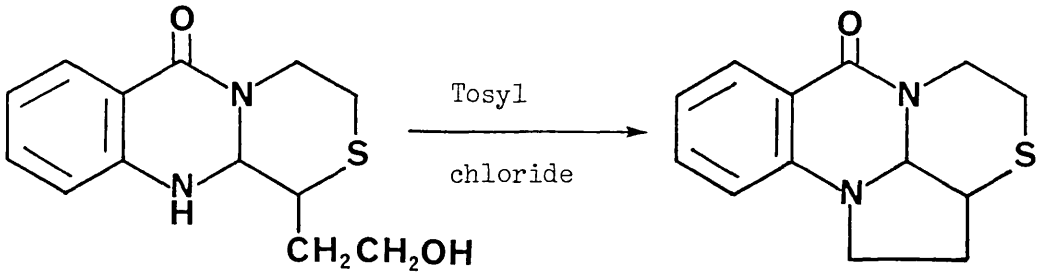
When a mixture of the heterocyclic ester (282) and anthranilic acid (24) was heated with phosphoryl chloride, the desired compound (280) was obtained in 47 % yield. (Scheme 68).



Scheme 68

Reduction of (280) with sodium borohydride in ethanol gave a compound which analysed as $C_{13}H_{16}N_2O_2S$. Infrared spectroscopy indicated no ester carbonyl and an amidic carbonyl at 1630 cm^{-1} (indicative of a reduced quinazolinone[89]). In the p.m.r. spectrum two exchangeable hydrogens were evident. After consideration of the above data the product was assigned structure (283). The employment of sodium borohydride, in large excess, in the preparation of alkanols from carboxylic acid esters has previously been reported[90]. Cyclodehydration of (283) using para-toluene sulphonyl chloride afforded the novel

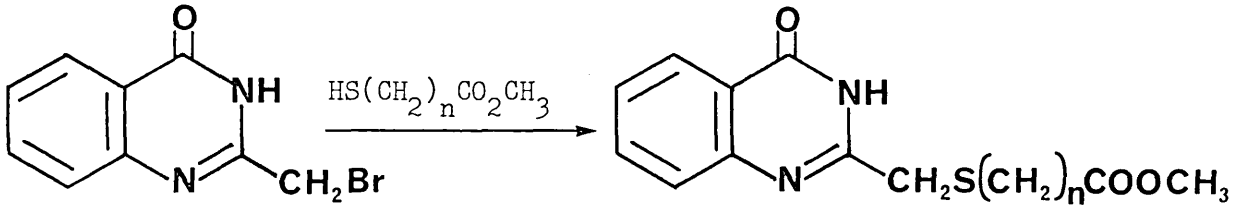
tetracyclic compound (284). (Scheme 69).



(283) (284)

Scheme 69

In an attempt to prepare novel thiazino[4,3-a] and thiazepino[4,3-a]quinazolinones the esters (286) and (287) were prepared by reaction of the bromomethylquinazolinone (285) with the thiolate anions derived from methyl thioglycolate (n = 1) and methyl mercaptopropionate (n = 2) respectively. (Scheme 70).



(285) (286) n = 1

(287) n = 2

Scheme 70

Attempted reduction of the esters (286) and (287) with sodium borohydride in ethanol led to complex mixtures which could only be partially resolved by column

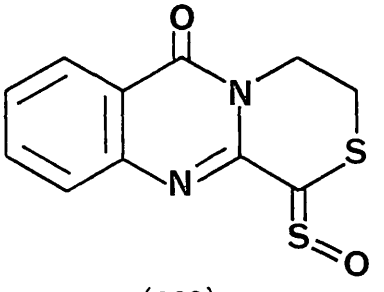
chromatography. Short path bulb to bulb distillation (Kugelrohr) of the crude oils obtained from these reactions resulted in decomposition of the material.

Halogenation

Although the chlorination of sulphoxides with thionyl chloride and acyl chlorides has been described, no reaction was observed between the sulphoxide (228) and thionyl chloride or benzoyl chloride. This is attributed to the extremely insoluble nature of the sulphoxide (228) in these reagents.

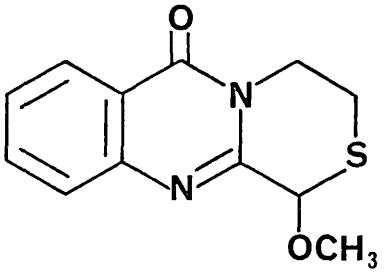
Attempted halogenation of the thiazinoquinazolinone (12) with sulphuryl chloride (SO_2Cl_2), N-bromosuccinimide and N-chlorosuccinimide proved unsuccessful.

The chlorination of dimethyl sulphide with thionyl chloride was reported in 1952 by Truce et al[91]. However when (12) was treated with this reagent, a compound which analysed for $C_{11}H_8N_2O_2S_2$ was obtained. P.m.r. indicated no protons at C-1. The compound was assigned structure (288).

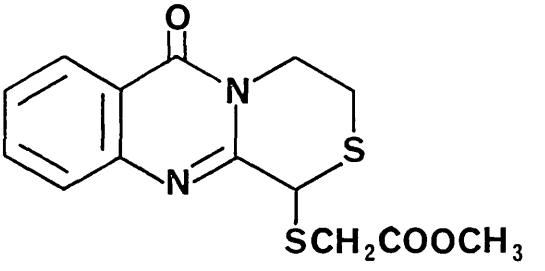


(288)

Bromination of (12) was accomplished, using N-bromosuccinimide in carbon tetrachloride in the presence of a free radical initiator, to give one major product which decomposed on column chromatography. The crude, unstable bromo compound could however be reacted directly with nucleophiles. For example, reaction with methoxide anion gave the methoxy derivative (289), whilst reaction with the thiolate anion derived from methyl thioglycolate (173) afforded the ester (290). Attempted reduction of the ester (290) with sodium borohydride in ethanol led to an extremely complex mixture from which no new products were isolated.



(289)



(290)

EXPERIMENTAL

General Methods

Spectroscopic Techniques

Infrared spectra were recorded for potassium bromide discs or as films on sodium chloride plates, using either a Perkin-Elmer 397 or Pye Unicam SP3-200 spectrophotometer. Proton magnetic resonance spectra were recorded in the appropriate solvent, using tetramethylsilane as internal standard, at 60 MHz on a Jeol JMN PMX 60 si spectrometer, or at 90 MHz on a Jeol FX90Q spectrometer.

Mass spectra were recorded with an AEI MS9 spectrometer at 70 eV.

Melting points are uncorrected and were determined using an electrothermal melting point apparatus.

Chromatographical Techniques

Absorption chromatography was carried out using silica gel (Merck, 70-230 mesh). Thin layer chromatography was conducted exclusively on pre-coated aluminium backed plates (Merck D.C., Alufolein, Kieselgel $60F_{254}$). Preparative layer chromatography was carried out using glass plates (20 x 20 cm) coated with silica gel (Kieselgel 60H) 2 mm thick. T.l.c. and p.l.c. plates, impregnated with a fluorescent indicator, were routinely developed by

ultraviolet irradiation. Development using a 0,5% aqueous potassium permanganate solution was occasionally employed.

Solvents

All solvents are reagent grade unless otherwise stated. Light petroleum refers to petroleum ether boiling range 60-80°C. Ether refers to diethyl ether. Tetrahydrofuran was dried by distillation from lithium aluminium hydride. Diethyl ether was dried over calcium chloride prior to storage over sodium wire. When necessary, chlorinated hydrocarbons were dried over calcium chloride. Aromatic solvents were dried over sodium wire or sodium/lead alloy prior to use.

Anhydrous magnesium sulphate was used as a standard drying agent for all organic solvents. Charcoal was routinely employed as a decolourising agent.

General Preparatory and Isolatory Techniques

Procedure (a) (fused quinazolinones)

The dark, viscous syrup was cautiously poured onto ice/water and made alkaline with concentrated ammonium hydroxide. The aqueous solution was extracted with dichloromethane (x4) and the combined extracts dried, decolourised and concentrated *in vacuo* to give the crude quinazolinone.

Procedure (b) (sulphoxides)

The reaction mixture was washed with saturated sodium metabisulphite solution (10 ml), then washed with dilute sodium hydroxide solution (10 ml). The dichloromethane layer was isolated, dried, decolourised and concentrated *in vacuo* to give the crude sulphoxide.

Procedure (c) (phenylmethylene derivatives)

The reaction mixture was cooled to 0°C and flooded with ether. Agitation induced crystallisation of the crude phenylmethylene derivative which was recrystallised, with decolourisation, from ethanol.

Procedure (d) (acetoxy derivatives)

The acetic anhydride was removed *in vacuo* and the residue dissolved in hot methanol, decolourised and filtered. Cooling to 0°C and agitation of the solution induced crystallisation of the acetoxy derivative, which was isolated by filtration and washed with a little cold methanol.

Procedure (e)

The reaction mixture was poured onto ice/water and extracted (x4) with dichloromethane. The combined extracts were washed with water (x2), dried, decolourised and concentrated *in vacuo*.

Procedure (f)

The methanol was evaporated *in vacuo* and the residue partitioned between dilute sulphuric acid (10 ml) and dichloromethane (100 ml). The dichloromethane layer was isolated, dried, decolourised and concentrated in vacuo.

* indicates known compound

Sulphur Containing Lactams

4-Thiazolidinone (113) *

Mercaptoacetamide (111) (5.00 g) was added to formalin (40%, 5 ml) and the resulting homogenous mixture stirred at room temperature for two hours. The solvent was removed in vacuo and the resulting viscous syrup subjected to vacuum distillation. A solid distilled, which was washed from the condenser with acetone. The resulting solution was dried, decolourised and filtered. Concentration of the solution in vacuo gave colourless needles of 4-thiazolidinone (113), (2.15 g, 38%) ; m.p. 98-99°C (reported m.p.[46] 98-99°C) ; $\bar{\nu}$max (KBr) : 3180 (N-H), 3080, 2900, 1665 (C=O), 1485, 1460, 1380, 1090 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.35(2H, s, -S-$\underline{CH_2}$-NH-), 4.27(2H, s, -S-$\underline{CH_2}$-CO-), 8.10(1H, broad s, D_2O exchangeable, >$\underline{NH}$).

3-Oxothiomorpholine (120) *

A solution of sodium methoxide (from 10.85 g of sodium in 150 ml of methanol) was added dropwise over one hour to a mixture of methyl thioglycolate (173) (25.00 g, 0.5 mol. equiv.) and 2-chloroethylamine hydrochloride (174) (27.30 g, 0.5 mol. equiv.) in methanol (200 ml). The mixture was stirred at ambient temperature for twenty four hours then the precipitated sodium chloride removed by filtration. The filtrate was concentrated in vacuo and the residue

treated with water (50 ml) prior to extraction with dichloromethane (3 x 50 ml). The combined extracts were dried, decolourised and concentrated *in vacuo* to afford a solid which was recrystallised from ethanol to give the pure title compound (120) as colourless prisms (20.10 g, 72%) ; m.p. 88-89°C (reported m.p.[50] 87-89°C) ; $\bar{\nu}$max (KBr) : 3260 (N-H), 2930, 1640 (C=O), 1620, 1490, 1340, 1115, 1015, 955 cm^{-1}.

4,5,6,7-Tetrahydro-1,4-thiazepin-3(2H)-one (134) *

A solution of sodium methoxide (from 9.23 g of sodium in 150 ml of methanol) was added dropwise over one hour to a mixture of methyl thioglycolate (173) (20.00 g, 0.5 mol. equiv.) and 3-chloropropylamine hydrochloride (175) (24.50 g, 0.5 mol. equiv.) in methanol (200 ml). The reaction mixture was stirred for twenty four hours, then the precipitated sodium chloride was removed by filtration. The filtrate was concentrated *in vacuo* and the residue treated with water (50 ml) prior to extraction with dichloromethane (3 x 50 ml). The combined extracts were dried, decolourised and concentrated *in vacuo* to give crude (134). Recrystallisation from ethanol gave the pure compound as colourless prisms, (13.20 g, 52%) ; m.p. 141-143°C (reported m.p.[53] 141-142.5°C) ; $\bar{\nu}$max (KBr) : 3240, 3100 (N-H), 2930, 2900, 1650 (C=O), 1480, 1420, 1360, 1150, 940 cm^{-1}.

2-Carbethoxymethyl-3-oxothiomorpholine (282)

A solution of sodium methoxide (prepared from sodium (4.6 g) in methanol (100 ml)) was added dropwise with ice cooling, over one hour, to a solution of ethyl mercaptosuccinate (281) (20.6 g, 0.5 mol. equiv.) and 2-chloroethyl-amine hydrochloride (11.6 g, 0.5 mol. equiv.) in methanol (150 ml). The reaction mixture was stirred at room temperature for twenty four hours then the precipitated sodium chloride was removed by filtration. The filtrate was concentrated *in vacuo* and the residue treated with water (50 ml) prior to extraction with dichloromethane (3 x 50 ml). The combined extracts were dried, decolourised, filtered and concentrated *in vacuo* to yield a colourless solid which was recrystallised from ethyl acetate/light petroleum, (9.75 g, 48%) ; m.p. 106-107°C ; $\bar{\nu}$max (KBr) : 3300 (N-H), 2975, 2925, 1740 (C=O ester), 1645 (C=O ring), 1615, 1490, 1335, 1175 (C-O ester), 960 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.54(3H, t, $-CH_2-\underline{CH_3}$), 2.51(4H, m, $-NH-CH_2-\underline{CH_2}-S-$, $-\underline{CH_2}-CO_2-$), 3.60 (3H, m, $-NH-\underline{CH_2}-CH_2-S-$, $>\underline{CH}-CH_2-CO_2-$), 4.15(2H, q, $-\underline{CH_2}-CH_3$), 7.48(1H, broad s, D_2O exchangeable).

Substituted 4-thiazolidinones

A mixture of the appropriate amide (thioglycolamide, 2-mercaptopropanamide or 2-mercapto-2-methyl-propanamide), 4 mole equivalents of acetone or acetaldehyde and

concentrated hydrochloric acid (1 ml) was warmed on a steam bath for one hour. The reaction mixture was cooled and the resulting precipitate isolated by filtration and recrystallised from water.

2-Methyl-4-thiazolidinone (252) *

From thioglycolamide and acetaldehyde, white powder, (34%) ; m.p. 300-302°C ; $\bar{\nu}$max (KBr) : 3380-3160 (N-H), 1650 (C=O), 1550 cm^{-1} ; δ(90 MHz, D_6DMSO) : 1.24(3H, d, >CH-$\underline{CH_3}$). 3.30(2H, s, -$\underline{CH_2}$-), 5.30(1H, m, >$\underline{CH}$-CH_3), 8.30 (1H, d, D_2O exchangeable, >N-$\underline{H}$) ; ^{m}/e 117 [$M^{+\cdot}$] (72%).

(Found : C 40.8, H 5.9, N 11.7, S 27.0. C_4H_7NOS requires C 41.0, H 6.0, N 11.9, S 27.4%).

2,2-Dimethyl-4-thiazolidinone (253) *

From thioglycolamide and acetone, colourless platelets, (70%) ; m.p. 125-126°C ; $\bar{\nu}$max (KBr) : 3400-3000 (N-H), 1700 (C=O), 1375 cm^{-1} ; δ(90 MHz, D_6DMSO) : 1.48(6H, s, C-2 methyl groups), 3.48(2H, s, -$\underline{CH_2}$-). 8.57(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; ^{m}/e 131 [$M^{+\cdot}$] (72%).

(Found : C 45.5, H 6.8, N 10.65, S 24.7. C_5H_9NOS requires C 45.8, H 6.9, N 10.7, S 24.4%).

2,5-Dimethyl-4-thiazolidinone (256) *

From 2-mercaptopropanamide and acetaldehyde, white powder ; m.p. 299-300°C ; (37%) ; $\bar{\nu}$max (KBr) ; 3380-3160 (N-H), 1650 (C=O), 1550 cm^{-1} ; $^{m}/e$ 131 [$M^{+\cdot}$] (57%).

(Found : C 45.7, H 6.8, N 10.6, S 23.9. C_5H_9NOS requires C 45.8, H 6.9, N 10.7, S 24.4%).

Due to the insoluble nature of this compound it was not possible to record its p.m.r. spectrum.

2,2,5-Trimethyl-4-thiazolidinone (254)

From 2-methyl-2-mercaptopropanamide and acetaldehyde, white powder (26%) ; m.p. 131-132°C ; $\bar{\nu}$max (KBr) : 3400-3000 (N-H), 1650 (C=O), 1430 cm^{-1} ; δ(90 MHz, D_6DMSO) : 1.32(3H, d, >CH-$\underline{CH_3}$), 1.49(6H, s, C-2 methyl groups), 4.84(1H, q, >$\underline{CH}$-CH_3), 8.59(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; $^{m}/e$ 145 [$M^{+\cdot}$] (49%).

(Found : C 49.7, H 7.6, N 9.7, S 21.9. $C_6H_{11}NOS$ requires C 49.6, H 7.6, N 9.6, S 22.1%).

2,2,5,5-Tetramethyl-4-thiazolidinone (255)

From 2-methyl-2-mercaptopropanamide and acetone, colourless platelets (79%) ; m.p. 201-202% ; $\bar{\nu}$max (KBr) : 3300-2900

(N-H), 1660 (C=O), 1620, 1400 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 1.56(6H, s, C-2 methyl groups), 1.66(6H, s, C-5 methyl groups), 7.27(1H, broad s, D_2O exchangeable, >N-H) ; $^m/_e$ 159 [$M^{+\cdot}$] (48%).

(Found : C 52.5, H 8.4, N 8.9, S 20.4. $C_7H_{13}NOS$ requires C 52.8, H 8.2, N 8.8, S 20.1%).

Fused Quinazolinones (11)-(13)

1H-Thiazolo[4,3-b]quinazolin-9(3H)-one (11)

Anthranilic acid (24) (15.72 g) and 4-thiazolidinone (113) (15.00 g, 1.25 mol. equiv.) were intimately mixed prior to the portionwise addition of phosphoryl chloride (40 ml). After subsidence of the resulting vigorous exothermic reaction the mixture was heated on a steam bath for one hour. The yellow solid obtained, following isolation using procedure (a), was recrystallised from ethyl acetate/light petroleum to give pure (11) as pale yellow needles, (13.92 g, 58%) ; m.p. 168-170°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.71 ; $\bar{\nu}$max (KBr) : 3075, 2960, 2925, 1680 (C=O), 1610 (C=N), 1560, 1470, 1380, 1330, 770, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 4.20(2H, s, >N-CH_2-S-$\underline{CH_2}$-), 5.08(2H, s, >N-$\underline{CH_2}$-S-CH_2-), 7.16-7.70(3H, m, aromatic protons), 8.10(1H, complex d, C-8-H), $^m/_e$ 204 [$M^{+\cdot}$].

(Found : C 58.7, H 3.9, N 13.7, S 15.6. $C_{10}H_8N_2OS$ requires C 58.8, H 3.9, N 13.7, S 15.7%).

3,4-Dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (12) *

Phosphoryl chloride (42 ml) was cautiously added to a mixture of anthranilic acid (24) (16.50 g) and 3-oxothiomorpholine (120) (17.87 g, 1.25 mol. equiv.).

After subsidence of the resulting vigorous exothermic reaction the mixture was heated on a steam bath for one hour. The oil isolated by procedure (a) was crystallised from ether and the resulting orange solid recrystallised from ethyl acetate/light petroleum to yield yellow prisms of pure (12), (14.75 g, 55%) ; m.p. 186-187°C (reported m.p.[41] 183°C) ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.69 ; $\bar{\nu}$max (KBr) : 3015, 2950, 2920, 1680 (C=O), 1605 (C=N), 1570, 1470, 1420, 1385, 780, 698 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.00(2H, t, J 6Hz, >N-CH_2-CH_2-S-), 3.75(2H, s, -S-CH_2-C=), 4.42(2H, t, J 6Hz, >N-CH_2-CH_2-S-), 7.35-7.90(3H, m, aromatic protons), 8.25(1H, complex d, C-7-H) ; ^{m}/e 218 [$M^{+\cdot}$] (85%).

(Found : C 60.25, H 4.7, N 12.8, S 14.7. $C_{11}H_{10}N_2OS$ requires C 60.6, H 4.6, N 12.8, S 14.7%).

1H-4,5-Dihydro-1,4-thiazepino[3,4-b]quinazolin-7(3H)-one (13)

Anthranilic acid (24) (11.70 g) and 4,5,6,7-tetrahydro-1,4-thiazepin-3(2H)-one (134) (14.00 g, 1.25 mol. equiv.) were intimately mixed prior to the portionwise addition of phosphoryl chloride (30 ml). After subsidence of the resulting vigorous exothermic reaction, the mixture was heated on a steam bath for one hour. The yellow solid obtained, following isolation using procedure (a), was recrystallised from ethyl acetate/light petroleum to yield the pure thiazepinoquinazolinone (13) as pale yellow prisms, (13.00 g, 65%), m.p. 156-157°C ; t.l.c. Rf(ethyl acetate/

triethylamine 9:1) 0.80 ; $\bar{\nu}$max (KBr) : 3050, 2950, 2925, 2900, 1675 (C=O), 1595 (C=N), 1470, 1390, 1330, 1145, 770, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.07(2H, m, >N-CH_2-CH_2-CH_2-S-), 2.83(2H, m, >N-CH_2-CH_2-CH_2-S-), 3.81(2H, s, -S-CH_2-C=), 4.07(2H, m, >N-CH_2-CH_2-CH_2-S-), 7.03-7.65(3H, m, aromatic protons), 8.02(1H, complex d, C-8-H) ; ^{m}/e 232 [$M^{+\cdot}$] (31%).

(Found : C 61.8, H 5.3, N 11.9, S 13.9. $C_{12}H_{12}N_2OS$ requires C 62.1, H 5.2, N 12.1, S 13.8%).

Substituted thiazolo[4,3-b]quinazolinones

1H-1-Methylthiazolo[4,3-b]quinazolin-9(3H)-one (243)

Anthranilic acid (24) (10.00 g) and 2-methyl-4-thiazolidinone (252) (10.67 g, 1.2 mol. equiv.) were intimately mixed prior to the portionwise addition of phosphoryl chloride (25 ml). The reaction mixture was then heated on a steam bath for one hour. The pale brown solid obtained by procedure (a) was recrystallised from ethyl acetate/light petroleum to give (243) as pale yellow prisms, (8.01 g, 50%) ; m.p. 152-154°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.70 ; $\bar{\nu}$max (KBr) : 3080, 3060, 2990, 2970, 1675 (C=O), 1610 (C=N), 1470, 1390, 1335, 775, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.79(3H, d, J 6Hz, >CH-CH_3), 4.02(1H, d, J 16Hz, =C-CH_2-S-), 4.48(1H, d, J 16Hz, =C-CH_2-S-), 5.78(1H, q, J 6Hz, >CH-CH_3), 7.14-7.74 (3H, m, aromatic protons), 8.15(1H, complex d, C-8-H) ;

$^{m}/e$ 218 [$M^{+\cdot}$] (79%).

(Found : C 60.7, H 4.7, N 12.9, S 14.8. $C_{11}H_{10}N_2OS$ requires C 60.55, H 4.6, N 12.8, S 14.7%).

1H-1,1-Dimethylthiazolo[4,3-b]quinazolin-9(3H)-one (244)

Phosphoryl chloride (25 ml) was cautiously added to a mixture of anthranilic acid (24) (10.00 g) and 2,2-dimethyl-4-thiazolidinone (253) (11.48 g, 1.2 mol. equiv.) and the mixture heated on a steam bath for one hour. Recrystallisation from ethanol of the yellow solid isolated using procedure (a) gave colourless prisms of (244), (7.53 g, 44%) ; m.p. 86-87°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.48 ; $\bar{\nu}$max (KBr) : 3020, 2990, 2945, 1680 (C=O), 1610 (C=N), 1475, 1335, 780, 700, 680 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.04(6H, s, $\chi\underline{CH_3}$), 4.14(2H, s, =C-$\underline{CH_2}$-S-), 7.20-7.75(3H, m, aromatic protons), 8.20(1H, complex d, C-8-H) ; $^{m}/e$ [$M^{+\cdot}$] 232 (58%).

(Found : C 61.9, H 5.35, N 12.1, S 14.15. $C_{12}H_{12}N_2OS$ requires C 62.05, H 5.2, N 12.1, S 13.8%).

1H-1,1,3-Trimethylthiazolo[4,3-b]quinazolin-9(3H)-one (245)

Phosphoryl chloride (6 ml) was cautiously added to a mixture of anthranilic acid (24) (2.30 g) and 2,2,5-trimethyl-4-

thiazolidinone (254) (2.90 g, 1.2 mol. equiv.) and the mixture heated on a steam bath for one hour. The brown solid isolated using procedure (a) was chromatographed on a column of silica gel (20 g). Elution with ethyl acetate/light petroleum (1:4) gave pure (245) as a pale yellow powder, (2.00 g, 48%). An analytical sample was prepared by recrystallisation from ethyl acetate/light petroleum ; m.p. 100-101°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.75 ; $\bar{\nu}$max (KBr) : 3050, 2980, 2940, 1675 (C=O), 1600 (C=N), 1470, 1380, 1330, 780, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.71(3H, d, J 6.6Hz, >CH-$\underline{CH_3}$), 1.96(3H, s, $\chi\frac{CH_3}{CH_3}$), 2.05(3H, s, $\chi\frac{CH_3}{\underline{CH_3}}$), 4.35(1H, q, J 6.6Hz, >$\underline{CH}$-CH_3), 7.10-7.70 (3H, m, aromatic protons), 8.10(1H, complex d, C-8-H) ; $^m/_e$ 246 [$M^{+\cdot}$] (100%).

(Found : C 63.6, H 5.8, N 11.4, S 13.1. $C_{13}H_{14}N_2OS$ requires C 63.4, H 5.7, N 11.4, S 13.0%).

1H-1,1,3,3-Tetramethylthiazolo[4,3-b]quinazolin-9(3H)-one (246)

Anthranilic acid (24) (4.80 g) and 2,2,5,5-tetramethyl-4-thiazolidinone (255) (6.80 g, 1.2 mol. equiv.) were thoroughly mixed prior to the portionwise addition of phosphoryl chloride (15 ml). The mixture was then heated on a steam bath for one hour. Procedure (a) furnished a solid which was isolated by filtration and washed with ether (x5). The solid (2.07 g) was identified as anthranilic

acid. The mother liquors were concentrated *in vacuo* and the residue chromatographed on a column of silica gel (50 g). Elution with ethyl acetate/light petroleum (1:4) afforded (246) as a pale yellow powder, (3.00 g, 32%). An analytical sample was prepared by recrystallisation from light petroleum ; m.p. 127-128°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.61 ; $\bar{\nu}$max (KBr) : 3055, 2975, 2925, 1675 (C=O) , 1600 (C=N), 1470, 1370, 1340, 1325, 1250, 775, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.78(6H, s, C-3 methyl groups), 2.06(6H, s, C-1 methyl groups), 7.10-7.70(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; $^m/e$ 260 [$M^{+\cdot}$] (100%).

(Found : C 64.85, H 6.3, N 10.8, S 12.6. $C_{14}H_{16}N_2OS$ requires C 64.6, H 6.15, N 10.75, S 12.3%).

1H-1,3-Dimethylthiazolo[4,3-b]quinazolin-9(3H)-ones (247a) and (247b)

Phosphoryl chloride (10 ml) was cautiously added to a mixture of anthranilic acid (24) (3.00 g) and 2,5-dimethyl-4-thiazolidinone (256) (3.49 g, 1.2 mol. equiv.). The reaction mixture was heated on a steam bath for one hour. Procedure (a) gave a dark red/brown oil which t.l.c. indicated consisted of two major components. The mixture was resolved by column chromatography, (75 g silica gel). Elution with ethyl acetate/light petroleum (1:9) afforded a pale yellow oil which was crystallised from ether/light

petroleum and recrystallised from ethyl acetate/light petroleum to give (247a) as pale yellow needles, (870 mg, 17%) ; m.p. 100-101°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.61 ; $\bar{\nu}$max (KBr) : 2970, 2930, 1670 (C=O), 1610 (C=N), 1470, 1380, 790, 705 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.72(3H, d, J 6.5Hz, >CH-$\underline{CH_3}$), 1.78(3H, d, J 6.5Hz, >CH-$\underline{CH_3}$), 4.58(1H, q, J 6.5Hz, >$\underline{CH}$-CH_3), 5.66(1H, q, J 6.5Hz, >CH-CH_3), 7.10-7.70(3H, m, aromatic protons), 8.10(1H, complex d, C-8-H) : ^{m}/e 232 [$M^{+\cdot}$] (100%).

(Found : C 61.8, H 5.1, N 11.85, S 13.7. $C_{12}H_{12}N_2OS$ requires 62.05, H 5.15, N 12.05, S 13.8%).

Further elution with the same solvent afforded (247b) as pale yellow needles following recrystallisation from ethyl acetate/light petroleum ; (1.30 g, 25%) ; m.p. 99-100°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.5 ; $\bar{\nu}$max (KBr) : 2975, 2925, 1680 (C=O), 1600 (C=N), 1470, 1380, 1260, 1220, 770, 695 cm^{-1} ; δ1.88(3H, d, J 6.7Hz, >CH-$\underline{CH_3}$), δ1.92(3H, d, J 5.7Hz, >CH-$\underline{CH_3}$), δ4.42(1H, q, J 6.7Hz, >$\underline{CH}$-CH_3), 5.66(1H, q, J 5.7Hz, >$\underline{CH}$-CH_3), 7.10-7.70(3H, m, aromatic protons), 8.14(1H, complex d, C-8-H) ; ^{m}/e 232 [$M^{+\cdot}$] (100%).

(Found : C 62.3, H 4.9, N 12.0, S 13.4. $C_{12}H_{12}N_2OS$ requires C 62.05, H 5.15, N 12.05, S 13.8%).

1H-1,3,3-Trimethylthiazolo[4,3-b]quinazolin-9(3H)-one (248)

A solution of the heterocycle (243) (3.44 g) and iodomethane (5.60 g, 2.5 mol. equiv.) in dry DMF (40 ml) was treated with sodium hydride (940 mg, 2.5 mol. equiv.). The mixture was stirred under a dry nitrogen atmosphere for one hour. Isolation using procedure (e) gave a red oil which was chromatographed on a column of silica gel (30 g). Elution with ethyl acetate/light petroleum (1:4) yielded the pure quinazolinone (248) as pale yellow plates, (2.73 g, 70.3%) ; m.p. 121-123°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.67 ; $\bar{\nu}$max (KBr) : 3050, 2975, 2920, 1660 (C=O), 1600 (C=N), 1460, 1380, 1360, 1170, 770, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.77(3H, s, $\chi\underline{CH_3}^{CH_3}$), 1.85(3H, s, $\chi_{\underline{CH_3}}^{CH_3}$), 1.89(3H, d, J 6.5Hz, >CH-$\underline{CH_3}$), 5.65(1H, q, J 6.5Hz, >$\underline{CH}$-CH_3), 7.20-7.80(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; ^{m}/e 246 [$M^{+\cdot}$] (76%).

(Found : C 63.3, H 5.9, N 11.3, S 12.6. $C_{13}H_{14}N_2OS$ requires C 63.4, H 5.7, N 11.4, S 13.0%).

1H-3,3-Dimethylthiazolo[4,3-b]quinazolin-9(3H)-one (249)

Sodium hydride (441 mg, 2.5 mol. equiv.) was added to a solution of the thiazoloquinazolinone (11) (1.50 g) and iodomethane (2.61 g, 2.5 mol. equiv.) in dry DMF (40 ml). The resulting deep red solution was stirred under a dry nitrogen atmosphere for two hours. Procedure (e) gave a

red oil which rapidly crystallised. Purification by column chromatography (20 g silica gel, ethyl acetate/light petroleum 1:9) furnished the desired compound (249) as colourless prisms, (970 mg, 56%) ; m.p. 114-115°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.48 ; $\bar{\nu}$max (KBr) : 3050, 2955, 1665 (C=O), 1610 (C=N), 1460, 775, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.78(6H, s, C-3 methyl groups), 5.06(2H, s, >N-$\underline{CH_2}$-S-), 7.20-7.75(3H, m, aromatic protons), 8.18(1H, complex d, C-8-H) ; $^m/e$ 232 [$M^{+\cdot}$] (74%).

(Found : C 62.2, H 5.2, N 12.1, S 13.4. $C_{12}H_{12}N_2OS$ requires C 62.05, H 5.15, N 12.05, S 13.8%).

1H-3-Methylthiazolo[4,3-b]quinazolin-9(3H)-one (250)

Sodium hydride (2.15 mg, 1.1 mol. equiv.) was added to a solution of the quinazolinone (11) (1.66 g) and iodomethane (1.27 g, 1.1 mol. equiv.) in dry DMF (40 ml). The resulting deep red solution was stirred for two hours under a dry nitrogen atmosphere. Procedure (e) afforded a three component mixture which was chromatographed on a column of silica gel (25 g). Elution with ether/light petroleum (1:9) gave the dimethyl derivative (249) (400 mg, 21%) identical in all respects (m.p., t.l.c., ir) to an authentic sample. Further elution with the same solvent system yielded (250) as a colourless crystalline solid, (580 mg, 32%) ; m.p. 90-91.5°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.54 ; $\bar{\nu}$max (KBr) : 2960, 2920, 1660 (C=O), 1605 (C=N), 1465,

1330, 780, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.76(3H, d, J 7.2Hz, >CH-$\underline{CH_3}$), 4.50(1H, q, J 7.2Hz, >$\underline{CH}$-CH_3), 4.94(1H, d, J 10.2Hz, >N-$\underline{CH_2}$-S-), 5.18(1H, d, J 10.2Hz, >N-$\underline{CH_2}$-S-), 7.20-7.76(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; $^{m}/e$ 218 [$M^{+\cdot}$] (100%).

(Found : C 60.5, H 4.35, N 12.7, S 14.5. $C_{11}H_{10}N_2OS$ requires C 60.55, H 4.6, N 12.85, S 14.7%).

Elution with ethyl acetate gave unreacted (11) (370 mg) identical in all respects (m.p., t.l.c., ir) to an authentic sample.

Phenylmethylene Derivatives

1H-3-Phenylmethylenethiazolo[4,3-b]quinazolin-9(3H)-one (185)

The thiazoloquinazolinone (11) (200 mg) and benzaldehyde (1 ml) were heated together at reflux temperature for one hour. The product was isolated, following procedure (c), as fine yellow needles, (110 mg, 38%) ; m.p. 223-225°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.83 ; $\bar{\nu}$max (KBr) : 3050, 1670 (C=O), 1610 (C=N), 1580, 1470, 1380, 775, 680 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 5.36(2H, s, >N-$\underline{CH_2}$-S-), 7.30-7.79(8H, m, aromatic protons), 8.00(1H, s, =<$^{Ph}_{\underline{H}}$), 8.28(1H, complex d, C-8-H) ; $^{m}/e$ 292 [$M^{+\cdot}$] (75%).

(Found : C 68.8, H 4.2, N 9.4, S 10.65. $C_{17}H_{12}N_2OS.\ \frac{1}{4}H_2O$ requires C 68.8, H 4.2, N 9.4, S 10.65%).

3,4-Dihydro-1-phenylmethylene-1,4-thiazino[3,4-b]-quinazolin-6(1H)-one (186)

The thiazinoquinazolinone (12) (200 mg) and benzaldehyde (1 ml) were heated together at reflux temperature for one hour. Isolation using procedure (c) afforded the product as large yellow prisms, (110 mg, 39%) ; m.p. 161-162°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.86 ; $\bar{\nu}$max (KBr) : 3050, 2940, 1670 (C=O), 1610 (C=N), 1540, 1470, 1380, 775, 690 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 3.20(2H, t, J 5.4Hz, >N-CH_2-$\underline{CH_2}$-S-), 4.55(2H, t, J 5.4Hz, >N-$\underline{CH_2}$-CH_2-S-), 7.33-7.83(9H, m, eight aromatic protons, $=<^{Ph}_{\underline{H}}$), 8.29(1H, complex d, C-7-H) ; $^m/_e$ 306 [$M^{+\cdot}$].

(Found : C 70.2, H 4.85, N 9.3, S 10.2. $C_{18}H_{14}N_2OS$ requires C 70.6, H 4.6, N 9.15, S 10.5%).

Attempted Condensation of (13) with Benzaldehyde

The thiazepinoquinazolinone (13) (200 mg) and benzaldehyde (1 ml) were heated together at reflux temperature for two hours. The reaction mixture was cooled and flooded with ether to give colourless needles of (13), identical in all respects (m.p., t.l.c., p.m.r., ir) to an authentic sample.

1H-1-Methyl-3-phenylmethylenethiazolo[4,3-b]quinazolin-9(3H)-one (257)

The compound (243) (580 mg) and benzaldehyde (2 ml) were heated together at reflux temperature for one hour. Isolation using procedure (c) afforded the pure benzylidene derivative as fine pale yellow needles, (660 mg, 81%) ; m.p. 179-180°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.54 ; $\bar{\nu}$max (KBr) : 3050, 1675 (C=O), 1580 (C=N), 1465, 1370, 770, 680 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.84(3H, d, J 6Hz, >CH-$\underline{CH_3}$), 5.90(1H, q, J 6Hz, >$\underline{CH}$-CH_3), 7.10-7.80(8H, m, aromatic protons), 7.88(1H, s, =<$^{Ph}_{\underline{H}}$), 8.18(1H, complex d, C-8-H) ; $^m/_e$ 306 [$M^{+\cdot}$] (62%).

(Found : C 70.7, H 4.6, N 9.5, S 10.4. $C_{18}H_{14}N_2OS$ requires C 70.6, H 4.55, N 9.15, S 10.45%).

1H-1,1-Dimethyl-3-phenylmethylenethiazolo[4,3-b]quinazolin-9(3H)-one (258)

A mixture of the quinazolinone (244) (650 mg) and benzaldehyde (2 ml) was heated at reflux temperature for one hour. Isolation using procedure (c) gave the pure phenylmethylene derivative as fine pale yellow needles, (600 mg, 67%) ; m.p. 180-181°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.61 ; $\bar{\nu}$max (KBr) : 3050, 2975, 2925, 1670 (C=O), 1600 (C=N), 1590, 1465, 1340, 1325, 770, 700, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.14(6H, s, C-1 methyl groups),

7.29-7.79(8H, m, aromatic protons), 7.86(1H, s, $=<^{Ph}_{H}$), 8.10(1H, complex d, C-8-H) ; $^{m}/e$ 320 [$M^{+\cdot}$] (100%).

(Found : C 71.1, H 5.0, N 9.0, S 10.3. $C_{19}H_{16}N_2OS$ requires C 71.25, H 5.0, N 8.75, S 10.0%).

Reactions with Electrophiles

3-(1-Acetoxyethylidene)-1H-thiazolo[4,3-b]quinazolin-9(3H)-one (187)

A mixture of (11) (2.00 g) and acetic anhydride (10 ml) was heated at reflux temperature for thirty hours, during which time extensive decomposition was observed. The mixture was cooled, the solvents removed in vacuo and the residue chromatographed on a column of silica gel (20 g). Elution with ethyl acetate/light petroleum (1:4) yielded the enol acetate (187), which was obtained as pale yellow needles after further purification by preparative t.l.c. (five plates), (460 mg, 16%) ; m.p. 148-149°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.21 ; $\bar{\nu}$max (KBr) : 3020, 1770 (C=O ester), 1670 (C=O ring), 1595 (C=N), 1470, 1370, 1080 (C-O ester), 780 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.26(3H, s, $-OCO\underline{CH_3}$), 2.72(3H, s, $=<^{O-}_{\underline{CH_3}}$), 5.19(2H, s, $>N-\underline{CH_2}-S-$), 7.36-7.78(3H, m, aromatic protons), 8.25(1H, complex d, C-8-H) ; $^{m}/e$ 288 [$M^{+\cdot}$] (18%).

(Found : C 58.0, H 3.9, N 9.5, S 11.3. $C_{14}H_{12}N_2O_3S$ requires C 58.3, H 4.15, N 9.7, S 11.1%).

3,4-Dihydro-1-(1-hydroxyethylidene)-1,4-thiazino[3,4-b] quinazolin-6(1H)-one (188)

A mixture of the quinazolinone (12) (2.00 g) and acetic anhydride (10 ml) was heated at reflux for twenty four hours. On cooling, the solution deposited a green solid which was removed by filtration, washed with a little cold ethanol and recrystallised from ethyl acetate/light petroleum to give the pure hydroxyethylidene derivative (188) as pale green needles, (560 mg, 23%) ; m.p. 210-212°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.71 ; $\bar{\nu}$max (KBr) : 2980, 2925, 1680 (C=O), 1620, 1580, 1430, 1370, 990, 780 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.24(3H, s, $=<^{OH}_{\underline{CH}_3}$), 3.05(2H, m, >N-$CH_2$-$\underline{CH}_2$-S-), 4.25(2H, m, >N-$\underline{CH}_2$-$CH_2$-S-), 7.20-7.77(3H, m, aromatic protons), 7.95(1H, complex d, C-7-H), 16.15(1H, broad s, D_2O exchangeable, enol proton) ; $^m/_e$ 260 [$M^{+\cdot}$] (100%).

(Found : C 60.15, H 4.7, N 10.7, S 12.1. $C_{13}H_{12}N_2O_2S$ requires C 60.0, H 4.6, N 10.8, S 12.3%).

Concentration of the filtrate in vacuo afforded unreacted (12) (600 mg) (identical in all respects to an authentic sample) following treatment of the residue with cold ethanol.

3-(1-Acetoxylethylidene)-1H-1-methylthiazolo[4,3-b] quinazolin-9(3H)-one (259)

The quinazolinone (243) (800 mg) and acetic anhydride (10 ml) were heated together at reflux for forty eight hours, during which time extensive decomposition was observed. The reaction mixture was cooled, the acetic anhydride removed *in vacuo* and the residue chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:9) afforded a yellow solid which was recrystallised from ethyl acetate/light petroleum to give the pure enol acetate (259) as a pale yellow powder, (210 mg, 19%) ; m.p. 148-150°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.48 ; $\bar{\nu}$max (KBr) : 2975, 2920, 1755 (C=O ester), 1675 (C=O ring), 1585 (C=N), 1460, 1380, 1170 (C-O ester), 770, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.80(3H, d, J 6Hz, >CH-$\underline{CH_3}$), 2.22(3H, s, -OCO$\underline{CH_3}$), 2.65 (3H, s, =<$\overset{O-}{\underset{CH_3}{}}$), 5.76(1H, q, J 6Hz, >$\underline{CH}$-$CH_3$), 7.10-7.70(3H, m, aromatic protons), 8.10(1H, complex d, C-8-H) ; $^m/_e$ 302 [$M^{+\cdot}$] (25%).

(Found : C 59.45, H 4.5, N 9.4, S 10.6. $C_{15}H_{14}N_2O_2S$ requires C 59.6, H 4.6, N 9.3, S 10.6%).

3-(1-Acetoxyethylidene)-1H-1,1-dimethylthiazolo[4,3-b] quinazolin-9(3H)-one (260)

A mixture of the quinazolinone (244) (1.02 g) and acetic anhydride (10 ml) was heated at reflux for fifty hours,

during which time considerable darkening of the material was observed. After cooling the reaction mixture, the acetic anhydride was evaporated *in vacuo* and the residue chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:9) gave a yellow oil which rapidly crystallised. Recrystallisation from light petroleum furnished the pure enol acetate as yellow needles, (330 mg, 23%) ; m.p. 125-126°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:3) 0.55 ; $\bar{\nu}$max (KBr) : 2980, 2940, 1760 (C=O ester), 1675 (C=O ring), 1590 (C=N), 1470, 1380, 1330, 1170 (C-O ester), 780, 700, 680 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.09(6H, s, C-1 methyl groups), 2.24(3H, s, $-OCOCH_3$), 2.73(3H, s, $=<^{O-}_{\underline{CH_3}}$), 7.36-7.75(3H, m, aromatic protons), 8.25(1H, complex d, C-8-H) ; $^m/e$ 316 [$M^{+\cdot}$] (28%).

(Found : C 60.6, H 5.1, N 9.05, S 10.1. $C_{16}H_{16}N_2O_3S$ requires C 60.75, H 5.05, N 8.85, S 10.1%).

3,4-Dihydro-1-(2,2,2-trifluoro-1-hydroxyethylidene)-1, 4-thiazino[3,4-b]quinazolin-6(1H)-one (190)

The thiazinoquinazolinone (12) (1.00 g) and trifluoroacetic anhydride (10 ml) were heated together until a homogenous solution was attained (one hundred hours). T.l.c. indicated no starting material. The trifluoroacetic anhydride was removed *in vacuo* and the residue crystallised on treatment with dichloromethane. The solid material was removed by filtration and washed with dichloromethane (x2), then with

ether (x2). Recrystallisation from methanol gave the pure title compound (190) as yellow needles, (1.13 g, 78%); m.p. 238-240°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.71 ; $\bar{\nu}$max (KBr) : 1695 (C=O), 1610 (C=N), 1570, 1195, 1120, 760 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.96(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.3(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 7.29-7.75(3H, m, aromatic protons), 8.20(1H, complex d, C-7-H) ; $^m/_e$ 314 [$M^{+\cdot}$] (100%).

(Found : C 49.3, H 3.0, N 9.0, S 9.9. $C_{13}H_9F_3N_2O_2S$ requires C 49.7, H 2.9, N 8.9, S 10.2%).

3,4-Dihydro-1-[1-(N-phenylaminoimino)ethyl]-1,4-thiazino [3,4-b]quinazolin-6(1H)-one (189)

A mixture of the enol (188) (160 mg), phenylhydrazine (130 mg, 2 mol. equiv.) and glacial acetic acid (four drops) in absolute ethanol (20 ml) was heated at reflux for thirty minutes. The solid which deposited on cooling was removed by filtration, washed with cold ethanol (x1) and with ether (x2). Recrystallisation from ethanol yielded the pure phenylhydrazone (189) as pale yellow needles, (180 mg, 85%) ; m.p. 202-203°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.50 ; $\bar{\nu}$max (KBr) : 3250 (N-H), 3050, 2925, 1675 (C=O), 1600 (C=N), 1470, 1250, 765, 700 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.06(3H, s, -$\underline{CH_3}$), 3.10(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.58(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 4.82(1H, s, =C-$\underline{CH}$-S-), 6.77-7.76(9H, m, eight aromatic protons,

=N-NH-Ph), 8.32(1H, complex d, C-7-H) ; $^{m}/e$ 350 [$M^{+\cdot}$] (100%).

(Found : C 64.9, H 5.1, N 16.0, S 9.0. $C_{19}H_{18}N_4OS$ requires C 65.15, H 5.15, N 16.0, S 9.15%).

Reaction of (190) with Phenylhydrazine

A mixture of the enol (190) (160 mg), phenylhydrazine (140 mg, 2 mol. equiv.) and glacial acetic acid (four drops) in absolute ethanol (20 ml) was heated for thirty minutes. The solid which deposited on cooling was isolated by filtration and washed with ether (x2). The product was identified as (12) and was identical in all respects (t.l.c., m.p., ir) to an authentic sample.

Reaction of (11) with Benzoyl Chloride

3-(Chlorophenylmethylene)-1H-thiazolo[4,3-b]quinazolin-9(3H)-one (191) and 3-(benzoyloxyphenylmethylene)-1H-thiazolo[4,3-b]quinazolin-9(3H)-one (192)

The thiazoloquinazolinone (11) (1.00 g) and benzoyl chloride (10 ml) were heated under reflux for one hour. The dark red reaction mixture was then cooled and chromatographed on a column of silica gel (50 g). Elution with ethyl acetate/light petroleum (1:9) gave the pure α-chlorobenzylidene derivative (191) as a pale yellow powder,

(110 mg, 7%) ; m.p. 184-185°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:4) 0.47 ; $\bar{\nu}$max (KBr) : 3060, 1685 (C=O), 1585 (C=N), 1470, 1365, 780, 755, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 5.26(2H, s, >N-$\underline{CH_2}$-S-), 7.07-7.70(8H, m, aromatic protons), 8.20(1H, complex d, C-8-H) ; ^{m}/e 326 (41%), 328 (14%) both [$M^{+\cdot}$].

(Found : C 62.4, H 3.0, N 8.4, S 9.8, Cl 10.9. $C_{17}H_{11}ClN_2OS$ requires C 62.5, H 3.4, N 8.6, S 9.8, Cl 10.9%).

Further elution of the column with ethyl acetate/light petroleum (1:5) afforded the enol benzoate (192) as pale yellow needles, (200 mg, 10%) ; m.p. 188-189°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.51 ; $\bar{\nu}$max (KBr) : 3070, 1740 (C=O ester), 1690 (C=O ring), 1580 (C=N), 1470, 1370, 1250 (C-O ester), 770, 710, 690 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 5.28(2H, s, >N-$\underline{CH_2}$-S-), 6.61(1H, m, aromatic proton), 7.28-7.83(10H, m, aromatic protons), 8.16-8.35 (3H, m, aromatic protons) ; ^{m}/e 412 [$M^{+\cdot}$] (16%).

(Found : C 69.8, H 4.1, N 7.0, S 7.8. $C_{24}H_{16}N_2O_3S$ requires C 69.9, H 3.9, N 6.8, S 7.8%).

<u>3-(2-Chloro-1-chloroacetoxyethylidene)-1H-thiazolo [4,3-b]quinazolin-9(3H)-one (194)</u>

A mixture of (11) (800 mg) and chloroacetyl chloride (10 ml) was heated at reflux for thirty minutes, during which time considerable decomposition appeared to have

occurred. The reaction mixture was cooled, the chloroacetyl chloride removed *in vacuo* and the residue chromatographed on a column of silica gel (20 g). Elution with ether/light petroleum (1:2) afforded a solid which was recrystallised from ethyl acetate/light petroleum to give pure (194), (120 mg, 8%) ; m.p. 148-149°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.21 ; $\bar{\nu}$max (KBr) : 3030, 2960, 1790 (C=O ester), 1670 (C=O ring), 1595 (C=N), 1470, 1370, 1140 (C-O ester), 785, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 4.13(0.35H, s, $-OCO\underline{CH_2}Cl$), 4.33(1.65H, s, $-OCO\underline{CH_2}Cl$), 5.25(2H, s, $>N-\underline{CH_2}-S-$), 5.34(0.35H, s, $=C-\underline{CH_2}Cl$), 5.42(1.65H, s, $=C-\underline{CH_2}-Cl$), 7.45-7.85(3H, m, aromatic protons), 8.28(1H, complex d, C-8-H) ; $^m/e$ 358 (16%), 356 (23%) both $[M^{+\cdot}]$.

(Found : C 47.5, H 3.0, N 8.1, S 9.1. $C_{14}H_{10}Cl_2N_2O_3S$ requires C 47.1, H 2.8, N 7.8, S 9.0%).

1-Carbethoxy-3,4-dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (195)

The compound (12) (2.00 g) and ethyl chloroformate (10 ml) were heated at 160°C for fifty hours, during which time extensive decomposition occurred. The cooled reaction mixture was extracted with dichloromethane (3 x 50 ml), the combined extracts concentrated *in vacuo* and the residue chromatographed on a column of silica gel (20 g). Elution with light petroleum/ether (3:1) afforded the ester, which

was recrystallised from ethyl acetate/light petroleum (3:1) to give pure (195) as colourless needles, (170 mg, 6%) ; m.p. 125-127°C ; t.l.c. Rf(ethyl acetate/ triethylamine 9:1) 0.82 ; $\bar{\nu}$max (KBr) : 2975, 1740 (C=O ester), 1675 (C=O ring), 1640, 1600(C=N), 1465, 1370, 1300, 1235 (C-O ester), 1050, 775, 755, 745 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.30(3H, t, J 7.2 Hz, $-CO_2CH_2\underline{CH_3}$), 2.96 (2H, m, $>N-CH_2-\underline{CH_2}-S-$), 4.18(2H, q, J 7.2Hz, $-CO_2\underline{CH_2}CH_3$), 4.19(2H, m, $>N-\underline{CH_2}-CH_2-S-$), 5.58(1H, s, $=\underline{C}-\underline{CH}-S-$), 6.90-7.70(3H, m, aromatic protons), 7.84(1H, complex d, C-7-H) ; $^m/_e$ 290 $[M^{+\cdot}]$ (59%).

(Found : C 57.6, H 4.4, N 9.5, S 11.0. $C_{14}H_{14}N_2O_3S$ requires C 57.9, H 4.4, N 9.5, S 11.0%).

3,4-Dihydro-1,1-dimethyl-1,4-thiazino[3,4-b]quinazolin 16(1H)-one (205)

A solution of the thiazinoquinazolinone (12) (1.00 g) and iodomethane (1.60 g, 2.5 mol. equiv.) in dry DMF (40 ml) was treated with sodium hydride (275 mg, 2.5 mol. equiv.). The mixture was stirred under a dry nitrogen atmosphere for sixteen hours. Procedure (e) afforded a brown solid which was chromatographed on a column of silica gel (20 g). Elution with ethyl acetate/light petroleum (1:4) yielded the dimethyl derivative (205) as pale yellow flakes, (650 mg, 58%) ; m.p. 128-129°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:3) 0.51 ; $\bar{\nu}$max (KBr) : 2950, 2920, 1660 (C=O), 1580(C=N), 1560, 1470, 1380, 1150, 765, 690 cm^{-1} ;

δ(60 MHz, $CDCl_3$) : 1.81(6H, s, C-1 methyl groups), 3.08 (2H, t, J 6Hz, >N-CH_2-$\underline{CH_2}$-S-), 4.50(2H, t, J 6Hz, >N-$\underline{CH_2}$-CH_2-S-), 7.20-7.70(3H, m, aromatic protons), 8.20 (1H, complex d, C-7-H) ; ^{m}/e 246 [$M^{+\cdot}$] (80%).

(Found : C 63.3, H 5.9, N 11.3, S 12.6. $C_{13}H_{14}N_2OS$ requires C 63.4, H 5.7, N 11.4, S 13.0%).

<u>1,1-Dibenzyl-3,4-dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (206)</u>

Sodium hydride (330 mg, 3 mol. equiv.) was added to a solution of the quinazolinone (12) (1.00 g) and benzyl bromide (2.30 g, 3 mol. equiv.) in dry DMF (40 ml). The reaction mixture was stirred for two hours then treated according to procedure (e). The orange syrup obtained was chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:9) afforded the pure dibenzyl compound (206) as a colourless crystalline solid, (1.06 g, 58%) ; m.p. 89-91°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:3) 0.55 ; $\bar{\nu}$max (KBr) : 3025, 2925, 1680 (C=O), 1610 (C=N), 1470, 1330, 1160, 780, 760, 730, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.10(2H, m, >N-CH_2- $\underline{CH_2}$-S-), 3.08(2H, d, J 14Hz), 3.75(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 3.96(2H, d, J 14Hz), 7.05(10H, s, aromatic protons), 7.20-7.80(3H, m, aromatic protons), 8.12(1H, complex d, C-7-H) ; ^{m}/e 398 [$M^{+\cdot}$] (7%).

(Found : C 75.1, H 5.7, N 6.95, S 7.7. $C_{25}H_{22}N_2O_2S$ requires C 75.4, H 5.5, N 7.05, S 8.05%).

Reactions with Heterocumulenes

1-H-1-[Bis(methylthio)]methylenethiazolo[4,3-b]quinazolin-9(3H)-one (196)

A solution of the quinazolinone (11) (1.00 g) and carbon disulphide (1.5 ml) in dry DMSO (30 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 580 mg, 2.5 mol. equiv.) was added portionwise and the resulting deep red solution stirred for one hour. Iodomethane (1.74 g, 2.5 mol. equiv.) was added dropwise and the mixture stirred a further one hour. The oil isolated by procedure (e) was chromatographed on a column of silica gel (25 g). Elution with ethyl acetate/light petroleum (1:3) afforded the ketene S,S-acetal (196). Recrystallisation from methanol/dichloromethane (1:1) gave the pure compound as lustrous orange flakes, (590 mg, 39%) ; 182-184°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.65 ; $\bar{\nu}$max (KBr) : 2930, 1670 (C=O), 1610, 1590 (C=N), 1470, 1365, 1050, 775, 770 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.48 (3H, s, Z -S-$\underline{CH_3}$), 2.58(3H, s, E -S-$\underline{CH_3}$), 5.22(2H, s, >N-$\underline{CH_2}$-S-), 7.37-7.86(3H, m, aromatic protons), 8.25(1H, complex d, C-8-H) ; $^m/e$ 308 [$M^{+\cdot}$] (100%).

(Found : C 50.4, H 3.9, N 9.0, S 31.0). $C_{13}H_{12}N_2OS_3$ requires C 50.6, H 3.9, N 9.1, S 31.5%).

3,4-Dihydro-1-[bis(methylthio)]methylene-1,4-thiazino [3,4-b]quinazolin-6(1H)-one (197)

A solution of the heterocycle (12) (1.00 g) and carbon disulphide (1.5 ml) in dry DMSO (30 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 550 mg, 2.5 mol. equiv.) was added portionwise and the resulting deep red solution stirred for one hour. Iodomethane (1.62 g, 2.5 mol. equiv.) was added dropwise and the mixture stirred a further one hour. Procedure (e) gave the crude product, which was chromatographed on a column of silica gel (25 g). Elution with ethyl acetate/ light petroleum (1:4) yielded, after recrystallisation from ethyl acetate/light petroleum, pure (197), (930 mg, 63%) as yellow needles ; m.p. 133-134°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.46 ; $\bar{\nu}$max (KBr) : 3080, 2950, 2930, 1680 (C=O), 1610 (C=N), 1580, 1565, 1470, 1375, 780, 700 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.38(3H, s, Z -S-$\underline{CH_3}$), 2.50(3H, s, E -S-$\underline{CH_3}$), 3.16(2H, t, J 5.25Hz, >N-CH_2-$\underline{CH_2}$-S-), 4.51(2H, t, J 5.25Hz, >N-$\underline{CH_2}$-CH_2-S-), 7.40-7.79(3H, m, aromatic protons), 8.30(1H, complex d, C-7-H) ; $^m/e$ 307 [$M^{+\cdot}$] (100%).

(Found : C 52.2, H 4.45, N 8.7, S 30.1. $C_{14}H_{14}N_2OS_3$ requires C 52.2, H 4.35, N 8.7, S 29.8%).

1H-4,5-Dihydro-1-[bis(methylthio)]methylene-1,4-thiazepino[3,4-b]quinazolin-7(3H)-one (198)

A solution of the compound (13) (1.00 g) and carbon disulphide (1.5 ml) in dry DMSO (40 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 520 mg, 2.5 mol. equiv.) was added portionwise and the resulting deep red solution stirred for one hour. Iodomethane (1.53 g, 2.5 mol. equiv.) was added dropwise and the mixture stirred a further one hour. The oil obtained using isolatory procedure (e) was chromatographed on a column of silica gel (25 g). Elution with ethyl acetate/light petroleum (1:4) afforded a pale yellow solid which was recrystallised from ethyl acetate/light petroleum to give pure (198) as colourless needles, (480 mg, 33%) ; m.p. 152-153°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.40 ; $\bar{\nu}$max (KBr) : 2970, 2930, 1680 (C=O), 1585 (C=N), 1470, 1380, 780 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.20(2H, broad, >N-CH_2-$\underline{CH_2}$-CH_2-), 2.31(3H, s, Z -S$\underline{CH_3}$), 2.48(3H, s, E -S-$\underline{CH_3}$), 2.80(2H, broad, >N-CH_2-$\underline{CH_2}$-CH_2-), 3.90(1H, broad, >N-$\underline{CH_2}$-CH_2-CH_2-), 4.90(1H, broad, >N-$\underline{CH_2}$-CH_2-CH_2-), 7.41-7.80(3H, m, aromatic protons), 8.30(1H, complex d, C-8-H) ; $^m/_e$ [$M^{+\cdot}$] (54%).

(Found : C 53.35, H 4.4, N 8.1, S 28.6. $C_{15}H_{16}N_2OS_3$ requires C 53.6, H 4.75, N 8.3, S 28.6%).

3,4-Dihydro-1-[bis(carbethoxymethylthio)]methylene-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (203)

Amixture of the thiazinoquinazolinone (12) (2.00 g), carbon disulphide (3 ml) and sodium hydride (550 mg, 2.5 mol. equiv.) in dry DMSO (50 ml) was stirred under a dry nitrogen atmosphere for one hour. Ethyl bromoacetate (3.36 g, 2.2 mol. equiv.) was added dropwise and the mixture stirred a further one hour. The red oil isolated by procedure (e) was chromatographed on a column of silica gel (40 g). Elution with ethyl acetate/light petroleum (1:4) gave the diester (203) as an unstable red oil, (3.20 g, 72%) ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.62 ; $\bar{\nu}$max (Neat) : 2975, 2925, 1730 (C=O ester), 1675 (C=O ring), 1580 (C=N), 1470, 1290, 1150 (C-O ester), 770, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.20(6H, m, $-CO_2-CH_2-\underline{CH_3}$, $-CO_2-CH_2-\underline{CH_3}$), 3.18(2H, m, $>N-CH_2-\underline{CH_2}-S-$), 3.50(2H, s, $-S-\underline{CH_2}-CO_2-$), 3.54(2H, s, $-S-\underline{CH_2}-CO_2-$), 4.00 (4H, m, $-CO_2-\underline{CH_2}-CH_3$, $-CO_2-\underline{CH_2}-CH_3$), 4.38(2H, m, $>N-\underline{CH_2}-CH_2-S-$), 7.10-7.80(3H, aromatic protons), 8.15(1H, complex d, C-7-H).

Reaction of the Ester (203) with Sodium Methoxide

The diester (203) (1.50 g) was dissolved in methanol (50 ml) and treated with sodium methoxide (260 mg, 1.5 mol. equiv.). The reaction mixture was warmed (steam bath) for six hours, then cooled and the precipitated

solid isolated by filtration. The highly insoluble yellow solid was washed thoroughly with hot methanol. The 1,3-dithiane (204) was obtained as a yellow powder, (750 mg, 54%) ; m.p. 187-189°C dec. ; $\bar{\nu}$max (KBr) : 3450 (C-H), 2950, 1670 (C=O ring and ester), 1610, 1555, 1450, 1380, 1230 (C-O ester), 770, 690 cm^{-1} ; δ(90 MHz, D_6DMSO) : 3.30(2H, m, >N-CH_2-CH_2-S-), 3.80(5H, m, -CO_2CH_3, -S-CH_2-C(=O)-OH), 4.44 (2H, m, >N-CH_2-CH_2-S-), 7.40-7.81(3H, m, aromatic protons), 8.10(1H, complex d, C-7-H) ; ^{m}/e 406 [$M^{+\cdot}$] (97%).

(Found : C 50.4, H 3.4, N 7.1, S 23.5. $C_{17}H_{14}N_2O_4S_3$ requires C 50.25, H 3.45, N 6.90, S 23.5%).

3-(Anilino-methylthiomethylene)-1H-thiazolo[4,3-b] quinazolin-9(3H)-one (199)

A solution of the quinazolinone (11) (1.00 g) and phenyl isothiocyanate (750 mg, 1.2 mol. equiv.) in dry DMSO (30 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 300 mg, 1.25 mol. equiv.) was added portionwise and the resulting deep green solution stirred for one hour. Iodomethane (750 mg, 1.1 mol. equiv.) was added dropwise and the mixture stirred a further one hour. Procedure (e) afforded the crude product which was chromatographed on a column of silica gel (15 g). Elution with ethyl acetate/light petroleum (1:9) furnished the pure S,N-acetal (199) as yellow needles, (940 mg, 59%) ; m.p. 147-148°C ; t.l.c.

Rf(ethyl acetate/light petroleum 1:3) 0.67 ; $\bar{\nu}$max (KBr) : 3030, 2930, 1680 (C=O), 1635, 1615, 1600, 1550, 1470, 1330, 770, 755 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.20(3H, s, -S-$\underline{CH_3}$), 5.26(2H, s, >N-$\underline{CH_2}$-S-), 7.00-7.75(8H, m, aromatic protons), 8.20(1H, complex d, C-8-H) ; ^{m}/e 353 [$M^{+\cdot}$] (88%).

(Found : C 61.45, H 4.4, N 12.2, S 18.1. $C_{18}H_{15}N_3OS_2$ requires C 61.2, H 4.25, N 11.8, S 17.8%).

<u>1-(Anilino-methylthiomethylene)-3,4-dihydro-1,4-thiazino [3,4-b]quinazolin-6(1H)-one (200)</u>

Sodium hydride (50% dispersion in oil, 280 mg, 1.3 mol. equiv.) was added to a solution of the quinazolinone (12) (1.00 g) and phenyl isothiocyanate (760 mg, 1.2 mol. equiv.) in dry DMSO (40 ml). The resulting deep green solution was stirred under a nitrogen atmosphere for one hour. Iodomethane (750 mg, 1.2 mol. equiv.) was added dropwise and the mixture stirred for a further one hour. The oil isolated by procedure (e) was chromatographed on a column of silica gel (15 g). Elution with ethyl acetate/ light petroleum (1;5) yielded (200) as a yellow crystalline solid, (730 mg, 43%) ; m.p. 179-181°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.42 and 0.71 (when the lower spot was removed and the upper re-run, two spots were again observed.) ; $\bar{\nu}$max (KBr) : 2950, 2930, 1680 (C=O), 1615

(C=N), 1530, 1470, 1350, 775, 760, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.19(2.5H, s, -S-$\underline{CH_3}$), 2.48(0.5H, s, -S-$\underline{CH_3}$), 3.10(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.51(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 6.95-7.78(8H, m, aromatic protons), 8.21(1H, complex d, C-7-H), 12.10(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; $^m/_e$ 367 [$M^{+\cdot}$] (10%).

(Found : C 62.0, H 4.5, N 11.45, S 17.3. $C_{19}H_{17}N_3OS_2$ requires C 62.1, H 4.6, N 11.4, S 17.4%).

<u>1-(Anilino-methylthiomethylene)-1H-4,5-dihydro-1,4-thiazepino[3,4-b]quinazolin-7(3H)-one (201)</u>

A solution of the heterocycle (12) (1.00 g) and phenyl isothiocyanate (700 mg, 1.2 mol. equiv.) in dry DMSO (40 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 250 mg, 1.2 mol. equiv.) was added portionwise and the resulting deep blue solution stirred for one hour. Iodomethane (730 mg, 1.2 mol. equiv.) was added and the mixture stirred a further one hour. The crude product obtained by procedure (e) was purified by column chromatography (15 g silica gel). Elution with ethyl acetate/light petroleum (1:9) afforded the pure ketene S,N-acetal (201) as an orange powder, (200 mg, 12%) ; m.p. 171-173°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.56 ; $\bar{\nu}$max (KBr) : 2900, 1670 (C=O), 1600 (C=N), 1520, 1460, 770, 750, 690 cm^{-1} ;

δ(60 MHz, $CDCl_3$) : 2.10(5H, m, -S-$\underline{CH_3}$, >N-CH_2-$\underline{CH_2}$-CH_2-), 2.80(2H, m, >N-CH_2-CH_2-$\underline{CH_2}$-), 4.36(2H, m, >N-$\underline{CH_2}$-CH_2-CH_2-), 6.60-7.80(8H, m, aromatic protons), 8.16(1H, complex d, C-8-H), 8.60(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; ^{m}/e 381 [$M^{+\cdot}$] (7%).

(Found : C 62.7, H 5.1, N 11.2, S 16.5. $C_{20}H_{19}N_3OS_2$ requires C 63.0, H 5.0, N 11.0, S 16.8%).

<u>1-(Anilino-carbethoxymethylthiomethylene)-3,4-dihydro-1, 4-thiazino[3,4-b]quinazolin-6(1H)-one (202)</u>

A solution of the thiazinoquinazolinone (12) (1.00 g) and phenyl isothiocyanate (750 mg, 1.2 mol. equiv.) in dry DMSO (40 ml) was stirred under a dry nitrogen atmosphere. Sodium hydride (50% dispersion in oil, 260 mg, 1.2 mol. equiv.) was added portionwise and the mixture stirred for one hour. Ethyl bromoacetate (920 mg, 1.2 mol. equiv.) was added dropwise and the mixture stirred for a further one hour. The syrup obtained by procedure (e) was chromatographed on a column of silica gel (25 g). Elution with ethyl acetate/light petroleum gave an orange oil which rapidly crystallised. The pure ester (202) was obtained as yellow needles following recrystallisation from n-hexane, (760 mg, 37%) ; m.p. 94-96°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:3) 0.30 ; $\bar{\nu}$max (KBr) : 3050, 2975, 2925, 1740 (C=O ester), 1680 (C=O ring), 1610 (C=N), 1550, 1470, 1200 (C-O ester), 775, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) :

1.20(3H, t, J 6.5Hz, $-CH_2-\underline{CH_3}$), 3.12(2H, m, $>N-CH_2-\underline{CH_2}-S-$), 3.36(2H, s, $-S-\underline{CH_2}-CO_2-$), 4.10(2H, q, J 6.5Hz, $-\underline{CH_2}-CH_3$), 4.50(2H, m, $>N-\underline{CH_2}-CH_2-S-$), 6.80-7.80(8H, m, aromatic protons), 8.20(1H, complex d, C-7-H), 11.80(1H, broad s, D_2O exchangeable, $>N-\underline{H}$) ; $^m/e$ 439 [$M^{+\cdot}$] (14%).

(Found : C 60.4, H 4.9, N 9.3, S 14.8. $C_{22}H_{21}N_3O_3S_2$ requires C 60.15, H 4.8, N 9.55, S 14.6%).

Reactions with Michael Acceptors

1-(2-Cyanoethyl)-3,4-dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (209)

A mixture of the thiazinoquinazolinone (12) (1.00 g) and acrylonitrile (730 mg, 3 mol. equiv.) in dry DMF (40 ml) was treated with sodium hydride (330 mg, 3 mol. equiv.). The reaction mixture was stirred for one hour then poured onto ice/water (250 ml) and acidified with dilute sulphuric acid. The aqueous solution was extracted with dichloromethane (4 x 50 ml) then the dried, combined extracts were concentrated in vacuo and the residue chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:4) afforded fine colourless needles of pure (209), (370 mg, 28%) ; m.p. 84-86°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.57 ; $\bar{\nu}$max (KBr) : 2950, 2925, 2250 (nitrile), 1680 (C=O), 1600 (C=N), 1470, 1390, 1150, 775, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.80-4.20

(8H, m, >N-CH-CH_2-S-, >CH-CH_2-CH_2-CN), 5.30(1H, m, >N-CH-CH_2-S-), 7.10-7.75(3H, m, aromatic protons), 8.18(1H, complex d, C-7-H) ; ^{m}/e 358 [$M^{+\cdot}$] (34%).

(Found : C 61.6, H 5.1, N 15.3, S 11.8. $C_{14}H_{13}N_3OS$ requires C 62.0, H 4.8, N 15.5, S 11.8%).

Reaction of (12) with Methyl Acrylate

A mixture of the thiazinoquinazolinone (12) (1.00 g) and methyl acrylate (470 mg, 1.2 mol. equiv.) in dry DMF (40 ml) was treated with sodium hydride (130 g, 1.2 mol. equiv.). After stirring for one hour the mixture was poured onto ice/water (250 ml), acidified with dilute sulphuric acid and the resulting solid isolated by filtration. The crude solid was dissolved in dichloromethane (5 ml) and chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:9) gave a colourless oil which rapidly crystallised to give the spiro compound (207) as colourless prisms, (450 mg, 27%) ; m.p. 105-107°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.63 ; $\bar{\nu}$max (KBr) : 2950, 1670 (C=O ring), 1660 (C=O αβ unsaturated ester), 1600 (C=N), 1560, 1470, 1280, 1210 (C-O ester), 770 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.00-2.80(4H, m, >C-CH_2-CH_2-C-OH), 2.85-3.20(4H, m, >C-CH_2-C-CO_2-, >N-CH_2-CH_2-S-), 3.75(3H, s, -CO_2-CH_3), 4.25(2H, m, >N-CH_2-CH_2-S-), 7.20-7.80(3H, m, aromatic protons), 8.20(1H, complex d, C-7-H), 12.30(1H, s,

D_2O exchangeable, -OH) ; $^m/e$ 358 [$M^{+\cdot}$] (34%).

(Found : C 60.6, H 5.1, N 7.7, S 9.0. $C_{18}H_{18}N_2O_4S$ requires C 60.3, H 5.0, N 7.8, S 8.9%).

Attempted Reaction of (12) with Methyl Vinyl Ketone

Sodium hydride (270 mg, 2.5 mol. equiv.) was added to a mixture of (12) (1.00 g) and methyl vinyl ketone (670 mg, 2.1 mol. equiv.) in dry DMF (40 ml). After stirring for one hour the mixture was poured onto ice/water (200 ml), acidified with dilute sulphuric acid and extracted with dichloromethane. T.l.c. of the extracts indicated no reaction had taken place, therefore the experiment was abandoned.

Attempted Reaction of (12) with Methyl Methacrylate

Sodium hydride (270 mg, 2.5 mol. equiv.) was added to a mixture of (12) (1.00 g) and methyl methacrylate (1.00 g, 2.2 mol. equiv.) in dry DMF (40 ml). After stirring for one hour the mixture was poured onto ice/water (200 ml), acidified with dilute sulphuric acid and extracted with dichloromethane. T.l.c. of the extracts indicated a complex mixture, the individual components of which could not be isolated.

Reactions with Activated Halopyridines

Reaction of (12) with 2-chloro-3-trifluoromethylpyridine

Sodium hydride (130 mg, 1.2 mol. equiv.) was added to a mixture of (12) (1.00 g) and 2-chloro-3-trifluoromethylpyridine (1.00 g, 1.2 mol. equiv.) in dry DMF (30 ml) under a dry nitrogen atmosphere. After stirring for three hours the reaction mixture was poured onto ice/water (250 ml) and extracted with ethyl acetate (4 x 50 ml). The combined extracts were washed with water (50 ml), dried and evaporated *in vacuo*. The residue yielded unreacted (12) (100 mg) on treatment with ether. The mother liquors were reconcentrated *in vacuo* and the residue chromatographed on a column of silica gel (15 g). Elution with ethyl acetate/light petroleum (1:4) gave a solid which was recrystallised from ethyl acetate/light petroleum to give the compound (210) as a white crystalline solid, (310 mg, 18%) ; m.p. 173-174°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.66 ; $\bar{\nu}$max (KBr) : 3055, 2925, 1675 (C=O), 1610, 1580, 1560, 1470, 1440, 1320, 770, 690 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 3.25(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.70(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 5.75(1H, s, =C-$\underline{CH}$-S), 7.34-7.77(4H, m, aromatic protons), 8.00(1H, m, aromatic proton), 8.28(1H, m, aromatic proton), 8.60(1H, m, aromatic proton) ; $^{m}/e$ 363 [$M^{+\cdot}$] (43%).

(Found : C 56.2, H 3.3, N 11.7, S 8.7. $C_{17}H_{12}F_3N_3OS$ requires C 56.2, H 3.3, N 11.55, S 8.8%).

Reaction of (12) with 2-chloro-3-cyanopyridine

A mixture of the thiazinoquinazolinone (12) (1.00 g) and 2-chloro-3-cyanopyridine (212) (700 mg 1.1 mol. equiv.) in dry DMSO (30 ml) was treated with sodium hydride (130 mg, 1.2 mol. equiv.). The reaction was stirred under a dry nitrogen atmosphere for one and a half hours then poured onto ice/water (250 ml) and extracted with dichloromethane (4 x 50 ml). The dried, combined extracts were concentrated in vacuo and the resulting red oil chromatographed on a column of silica gel (25 g). Elution with ether/light petroleum (1:3) gave unreacted quinazolinone (350 mg) and chlorocyanopyridine (250 mg). Elution with ether afforded the minor product (218) as a pale yellow powder (170 mg, 11%) ; m.p. 174-176°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.50 ; $\bar{\nu}$max (KBr) : 3050, 2995, 2940, 2225 (nitrile), 1670 (C=O), 1610, 1600, 1580, 1560, 1460, 1340, 780, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.12(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.52(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 5.64(1H, s, =C-$\underline{CH}$-S-), 7.10-8.40(7H, m, aromatic protons) ; ^{m}/e 320 [$M^{+\cdot}$] (3.5%).

(Found : C 64.1, H 3.6, N 17.4, S 9.9. $C_{17}H_{12}N_4OS$ requires C 63.75, H 3.75, N 17.5, S 10.0%).

Elution with ethyl acetate afforded the major product (219) as an orange powder, (400 mg, 27%) ; m.p. 177-178°C ; t.l.c. Rf (ethyl acetate/light petroleum 1:1) 0.25 ;

$\bar{\nu}$max (KBr) : 3250 (=N-H), 1670 (C=O), 1620, 1600, 1570, 1540, 1465, 1380, 780, 750 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.10(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.38(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 6.95-8.65(8H, m, 1H D_2O exchangeable, aromatic protons, =N-$\underline{H}$) ; ^{m}/e 320 [$M^{+\cdot}$] (100%).

(Found : C 63.4, H 3.8, N 17.1, S 9.7. $C_{17}H_{12}N_4OS$ requires C 63.75, H 3.75, N 17.5, S 10.0%).

Reaction of (12) with 4-chloro-3-cyanopyridine

A mixture of the thiazinoquinazolinone (12) (1.00 g) and 4-chloro-3-cyanopyridine (215) (700 mg, 1:1mol. equiv.) in dry DMSO (30 ml) was treated with sodium hydride (240 mg, 2.2 mol. equiv.). The reaction mixture was stirred under a nitrogen atmosphere for one and a half hours then poured onto ice/water (250 ml) and extracted with dichloromethane (4 x 50 ml). The dried, combined extracts were concentrated in vacuo to give a brown solid. Recrystallisation from dichloromethane/ether, following decolourisation, afforded the compound (220) as an orange solid, (500 mg, 34%) ; m.p. 179-181°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.55 ; $\bar{\nu}$max (KBr) : 3265 (=N-H), 1665 (C=O), 1640, 1580, 1560, 1530, 1460, 1385, 1300, 760 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 3.20(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.35(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 7.20-8.80(8H, m, aromatic protons, =N-$\underline{H}$) ; ^{m}/e 320 [$M^{+\cdot}$] (100%).

(Found : C 63.9, H 3.65, N 17.3, S 10.2. $C_{17}H_{12}N_4OS$ requires C 63.75, H 3.75, N 17.5, S 10.0%).

Attempted Reaction of (12) with 3-chloro-2-cyanopyridine

A mixture of the quinazolinone (12) (1.00 g) and 3-chloro-2-cyanopyridine (217) (700 mg 1.1 mol. equiv.) in dry DMSO (30 ml) was treated with sodium hydride (240 mg, 2.2 mol. equiv.). The reaction mixture was stirred for two hours then poured onto ice/water (250 ml). T.l.c. of dichloromethane extracts indicated only starting materials therefore the experiment was abandoned.

Sulphoxides

1H-2-Oxothiazolo[4,3-b]quinazolin-9(3H)-one (227)

3-Chloroperoxybenzoic acid (1.00 g, 1.1 mol. equiv.) was added portionwise to an ice cold, stirred solution of (11) (1.00 g) in dichloromethane (50 ml). The solution was stirred at room temperature for thirty minutes. Procedure (b) afforded the crude sulphoxide (227), which was obtained as colourless needles, following recrystallisation from ethyl acetate, (530 mg, 49%) : m.p. 194-195°C. dec. ; t.l.c. Rf(ethyl acetate/ triethylamine 9:1) 0.25 ; $\bar{\nu}$max (KBr) : 3050, 2930, 2920, 1685 (C=O), 1620, 1610 (C=N), 1470, 1435, 1335, 1045 (S=O), 780, 700, 680 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 4.30(2H,

s, -SO-$\underline{CH_2}$-C=), 4.95(1H, d, J 13.7Hz, >N-$\underline{CH_2}$-SO-), 5.40 (1H, d, J 13.7Hz, >N-$\underline{CH_2}$-SO-), 7.42-7.79(3H, m, aromatic protons), 8.28(1H, complex d, C-8-H) ; ^{m}/e 220 [$M^{+\cdot}$] (36%).

(Found : C 54.2, H 3.6, N 12.4, S 14.8. $C_{10}H_8N_2O_2S$ requires C 54.5, H 3.6, N 12.7, S 14.5%).

3,4-Dihydro-2-oxo-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (228)

A solution of (12) (1.92 g) in dichloromethane (50 ml) was chilled and 3-chloroperoxybenzoic acid (1.86 g, 1.08 mol. equiv.) added portionwise. The reaction mixture was stirred at room temperature for thirty minutes then the resulting precipitate removed by filtration. Washing the solid several times with hot methanol gave the pure sulphoxide (228) as a white powder, (1.67 g, 81%) ; m.p. 212-214°C dec. $\bar{\nu}$max (KBr) : 3000, 2935, 1680 (C=O), 1605 (C=N), 1475, 1410, 1385, 1030 (S=O), 700 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.80(2H, m, -SO-$\underline{CH_2}$-C=), 3.80-4.90(4H, m, >N-$\underline{CH_2}$-$\underline{CH_2}$-SO-), 7.42-7.91(3H, m, aromatic protons), 8.16 (1H, complex d, C-7-H) ; ^{m}/e 234 [$M^{+\cdot}$] (40%).

(Found : C 55.35, H 4.4, N 11.75, S 13.5. $C_{11}H_{10}N_2O_2S.{}^{1}/_{4}H_2O$ requires C 55.4, H 4.4, N 12.0, S 13.35%).

1H-4,5-Dihydro-2-oxo-1,4-thiazepino[3,4-b]quinazolin-7(3H)-one (229)

3-Chloroperoxybenzoic acid (1.95 g, 1.1 mol. equiv.) was added portionwise to an ice cold, stirred solution of the thiazepinoquinazolinone (13) (2.00 g) in dichloromethane (50 ml). The reaction mixture was stirred at room temperature for one hour, then the resulting precipitate removed by filtration. Washing the solid several times with hot methanol gave the pure sulphoxide (229) as a white powder, (1.73 g, 81%) ; m.p. 271-272°C dec. ; $\bar{\nu}$max (KBr) : 2990, 2950, 2920, 1680 (C=O), 1610, 1590 (C=N), 1480, 1395, 1025, 1020 (S=O), 775, 700 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.15(2H, m, >N-CH_2-$\underline{CH_2}$-CH_2-), 3.20(2H, m, >N-CH_2-CH_2-$\underline{CH_2}$-), 4.18(1H, m, >N-$\underline{CH_2}$-CH_2-CH_2-), 4.67(2H, AB quartet, J 13.3Hz, -SO-$\underline{CH_2}$-C=), 4.80(1H, m, >N-$\underline{CH_2}$-CH_2-CH_2-), 7.48-7.79(3H, m, aromatic protons), 8.08 (1H, complex d, C-8-H) ; ^{m}/e 248 [$M^{+\cdot}$] (10%).

(Found : C 57.8, H 4.9, N 11.2, S 12.7. $C_{12}H_{12}N_2O_2S$ requires C 58.1, H 4.8, N 11.3, S 12.9%).

1-Acetoxy-3,4-dihydro-2-oxo-1,4-thiazino[3,4-b]-quinazolin-6(1H)-one (239)

An ice cold solution of the aceotxy derivative (231) (1.10 g) in chloroform (50 ml) was treated with 3-chloroperoxybenzoic acid (0.90 g, 1.08 mol. equiv.).

After stirring at room temperature for one hour the resulting precipitate was isolated by filtration. Washing the solid with hot methanol gave the pure sulphoxide (239) as a white powder, (700 mg, 67%) ; m.p. 214-216°C ; $\bar{\nu}$max (KBr) : 3030, 3000, 2935, 1760 (C=O ester), 1685 (C=O ring), 1610 (C=N), 1470, 1395, 1225 (C-O ester), 1035 (S=O), 770, 695 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.28(3H, s, OCO$\underline{CH_3}$), 3.27-4.67(5H, m, >N-$\underline{CH_2}$-$\underline{CH_2}$-SO-, >$\underline{CH}$-O-), 7.55-7.86(3H, m, aromatic protons), 8.16(1H, complex d, C-7-H) ; ^{m}/e 250 [$M^{+\cdot}$] (100%).

(Found : C 53.4, H 4.1, N 9.6, S 10.95. $C_{13}H_{12}N_2O_4S$ requires C 53.1, H 4.1, N 9.6, S 10.55%).

1H-1-Methyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (261)

3-Chloroperoxybenzoic acid (1.80 g, 1.1 mol. equiv.) was added in small portions to an ice cold, stirred solution of the heterocycle (243) (1.80 g) in dichloromethane (30 ml). The reaction mixture was stirred for thirty minutes then treated according to procedure (b). The crude sulphoxide was recrystallised from ethyl acetate/ light petroleum to give colourless prisms of (261), (220 mg, 68%) ; m.p. 185-187°C ; t.l.c. Rf(ethyl acetate/ triethylamine 9:1) 0.36 ; $\bar{\nu}$max (KBr) : 2970, 2940, 1680 (C=O), 1625 (C=N), 1475, 1340, 1055 (S=O), 785 cm^{-1} ; δ(60 MHz, D_6DMSO) : 1.60(3H, d, J 7Hz, >CH-$\underline{CH_3}$), 4.22(2H, AB quartet, J 16.8Hz, -SO-$\underline{CH_2}$-C=), 5.58(1H, q, J 7Hz,

>CH-CH_3), 7.10-7.80(3H, m, aromatic protons), 8.10(1H, complex d, C-8-H) ; ^{m}/e 234 [$M^{+\cdot}$] (42%).

(Found : C 56.3, H 4.3, N 11.8, S 13.8. $C_{11}H_{10}N_2O_2S$ requires C 56.4, H 4.25, N 11.95, S 13.65%).

1H-1,1-Dimethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (262)

3-Chloroperoxybenzoic acid (4.72 g, 1.1 mol. equiv.) was added portionwise to a stirred, ice cold solution of (244) (5.00 g) in dichloromethane (75 ml). The reaction mixture was stirred at room temperature for thirty minutes. Isolation using procedure (b) gave the crude sulphoxide, which was obtained as colourless needles following recrystallisation from methanol, (3.95 g, 74%) ; m.p. 191-192°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.40 ; $\bar{\nu}$max (KBr) : 3020, 2995, 2900, 1690 (C=O), 1615 (C=N), 1480, 1350, 1065 (S=O), 780, 705, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.75(3H, s, $\chi^{CH_3}_{CH_3}$), 2.10(3H, s, $\chi^{CH_3}_{CH_3}$), 4.15(2H, AB quartet, -S-CH_2-C=), 7.15-7.70(3H, m, aromatic protons), 8.10(1H, complex d, C-8-H) ; ^{m}/e 248 [$M^{+\cdot}$] (100%).

(Found : C 58.1, H 4.9, N 11.1, S 13.2. $C_{12}H_{12}N_2O_2S$ requires C 58.05, H 4.8, N 11.3, S 12.9%).

1H, 1,1,3-Trimethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (263)

3-Chloroperoxybenzoic acid (950 mg, 1.1 mol. equiv.) was added portionwise to a stirred ice cold solution of the heterocycle (245) (800 mg) in dichloromethane (50 ml). The reaction was stirred at ambient temperature for thirty minutes. The orange syrup obtained by procedure (b) was crystallised from ether. Recrystallisation from ethanol furnished colourless platelets of the pure sulphoxide (263), (620 mg, 78%) ; m.p. 203-205°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.45 ; $\bar{\nu}$max (KBr) : 2980, 2930, 1665 (C=O), 1610 (C=N), 1470, 1330, 1300, 1060 (S=O), 780, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 1.80(3H, s, $\chi^{CH_3}_{\underline{CH_3}}$), 1.86 (3H, d, J 7Hz, >CH-$\underline{CH_3}$), 2.14(3H, s, $\chi^{CH_3}_{\underline{CH_3}}$), 4.07(1H, q, J 7Hz, >$\underline{CH}$-$CH_3$), 7.37-7.85(3H, m, aromatic protons), 8.25 (1H, complex d, C-8-H) ; ^{m}/e 262 [$M^{+\cdot}$] (12%).

(Found : C 59.3, H 5.4, N 10.4, S 12.3. $C_{13}H_{14}N_2O_2S$ requires C 59.55, H 5.35, N 10.7, S 12.2%).

1H-1,1,3,3-Tetramethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (264)

3-Chloroperoxybenzoic acid (2.20 g, 1.1 mol. equiv.) was added portionwise to a stirred ice cold solution of the quinazolinone (246) (2.60 g) in dichloromethane (50 ml). The mixture was stirred at room temperature for thirty

minutes. The solid obtained following procedure (b) was recrystallised from ethyl acetate/light petroleum to give the pure sulphoxide (264) as colourless needles, (1.95 g, 70%) ; m.p. 163-164°C ; t.l.c. Rf(ethyl acetate/ triethylamine 9:1) 0.71 ; $\bar{\nu}$max (KBr) : 2975, 2925, 1685 (C=O), 1600 (C=N), 1470, 1060 (S=O), 770, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.68(3H, s, C-3 methyl group), 1.76 (3H, s, C-3 methyl group), 1.98(6H, s, C-1 methyl groups), 7.20-7.80(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; $^m/e$ 276 [$M^{+\cdot}$] (39%).

(Found : C 61.3, H 6.0, N 9.8, S 11.4. $C_{14}H_{16}N_2O_2S$ requires C 60.9, H 5.8, N 10.15, S 11.6%).

1H-1,3-Dimethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (265)

A solution of the heterocycle (247b) (1.00 g) in dichloromethane (50 ml) was chilled and 3-chloroperoxybenzoic acid (950 mg, 1.1 mol. equiv.) added portionwise with stirring. The mixture was then stirred at room temperature for thirty minutes. Procedure (b) gave the crude sulphoxide (265) as a pale orange solid which was recrystallised from ethanol to give the pure compound as pale yellow needles, (840 mg, 78%) ; m.p. 190-191°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.53 ; $\bar{\nu}$max (KBr) : 2985, 2945, 1675 (C=O), 1610 (C=N), 1470, 1370, 1330, 1060 (S=O), 780, 695 cm^{-1} ; δ(60 MHz,

$CDCl_3$) : 1.63(3H, d, J 7.2Hz, >CH-$\underline{CH_3}$), 1.81(3H, d, J 7.2Hz, >CH-$\underline{CH_3}$), 4.11(1H, q, J 7.2Hz, >$\underline{CH}$-CH_3), 5.42 (1H, q, J 7.2Hz, >$\underline{CH}$-CH_3), 7.15-7.70(3H, m, aromatic protons), 8.15(1H, complex d, C-8-H) ; ^{m}/e 248 [$M^{+\cdot}$] (43%).

(Found : C 58.1, H 4.9, N 11.1, S 13.2. $C_{12}H_{12}N_2O_2S$ requires C 58.05, H 4.8, N 11.3, S 12.9%).

1H-1,3,3-Trimethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H) -one (266)

3-Chloroperoxybenzoic acid (1.89 g, 1.1 mol. equiv.) was added portionwise to an ice cold solution of the quinazolinone (248) (2.10 g) in dichloromethane (50 ml). The reaction mixture was stirred at room temperature for thirty minutes. The solid obtained by procedure (b) was recrystallised from ethyl acetate/light petroleum to give the pure sulphoxide (266) as pale yellow prisms, (1.74 g, 78%) ; m.p. 200-202°C ; t.l.c. Rf(ethyl acetate/ triethylamine 9:1) 0.47 ; $\bar{\nu}$max (KBr) : 3050, 2955, 2920, 1680 (C=O), 1610 (C=N), 1460, 1055 (S=O), 780, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.64(3H, s, C-3 methyl group), 1.80(3H, s, C-3 methyl group), 1.86(3H, d, J 7.2Hz, >CH-$\underline{CH_3}$), 5.30 (1H, q, J 7.2Hz, >$\underline{CH}$-CH_3), 7.15-7.75(3H, m, aromatic protons), 8.15(1H, complex d, C-8-H) ; ^{m}/e 262 [$M^{+\cdot}$] (44%).

(Found : C 59.3, H 5.25, N 10.75, S 11.9. $C_{13}H_{14}N_2O_2S$ requires C 59.55, H 5.35, N 10.7, S 12.2%).

1H-3,3-Dimethyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (267)

3-Chloroperoxybenzoic acid (1.00 g, 1.1 mol. equiv.) was added portionwise to an ice cold stirred solution of the heterocycle (249) (1.00 g) in dichloromethane (50 ml). The mixture was stirred at room temperature for thirty minutes. Procedure (b) afforded a solid which was purified by column chromatography (10 g silica gel). Elution with ether/light petroleum (1:3) yielded the desired sulphoxide (267) as colourless prisms, (860 mg, 80.5%) ; m.p. 181-182°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.54 ; $\bar{\nu}$max (KBr) : 3040, 2980, 2925, 1675 (C=O), 1600 (C=N), 1465, 1380, 1060 (S=O), 770 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.52(3H, s, C-3 methyl group), 1.82(3H, s, C-3 methyl group), 5.02(2H, AB quartet, J 13.8Hz, >N-$\underline{CH_2}$-SO-), 7.10-7.68(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; $^m/_e$ 248 [$M^{+\cdot}$] (43%).

(Found : C 57.6, H 4.9, N 11.1, S 12.6. $C_{12}H_{12}N_2O_2S$ requires C 58.05, H 4.8, N 11.3, S 12.9%).

1H-3-Methyl-2-oxothiazolo[4,3-b]quinazolin-9(3H)-one (268)

A solution of the quinazolinone (250) (300 mg) in dichloromethane (30 ml) was cooled prior to the portionwise addition of 3-chloroperoxybenzoic acid (300 mg, 1.1 mol. equiv.), then stirred at room temperature for thirty minutes. Procedure (b) afforded the crude sulphoxide which was recrystallised from ethyl acetate/ light petroleum to give pure (268) as small colourless prisms, (220 mg, 68%) ; m.p. 187-189.5°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.36 ; $\bar{\nu}$max (KBr) : 2980, 2900, 1670 (C=O), 1610 (C=N), 1460, 1360, 1060 (S=O), 780, 725 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 1.85(3H, d, J 7.1Hz, >CH-$\underline{CH_3}$), 4.12(1H, q, J 7.1Hz, >$\underline{CH}$-CH_3), 5.10(1H, AB quartet, J 13.5Hz, >N-$\underline{CH_2}$-SO-), 7.41-7.80(3H, m, aromatic protons), 8.25(1H, complex d, C-8-H) ; ^{m}/e 234 [$M^{+\cdot}$] (43%).

(Found : C 56.0, H 4.1, N 12.0, S 13.5. $C_{11}H_{10}N_2O_2S$ requires C 56.4, H 4.25, N 11.95, S 13.65%).

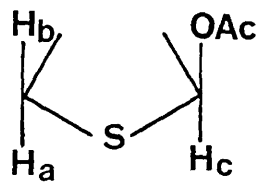
Pummerer Rearrangements

3-Acetoxy-1H-thiazolo[4,3-b]quinazolin-9(3H)-one (230)

The sulphoxide (227) (600 mg) and acetic anhydride (10 ml) were heated at reflux for one hour, during which time considerable darkening of the reaction mixture was

observed. Isolation by procedure (d) and recrystallisation from ethanol gave the title compound as a white powder, (150 mg, 21%) ; m.p. 133.5-134.5°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.73 ; $\bar{\nu}$max (KBr) : 2975, 1740 (C=O, ester), 1680 (C=O ring), 1620, 1610 (C=N), 1470, 1380, 1225 (C-O ester), 1020, 970, 770, 690 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.17(3H, s, $-OCO\underline{CH_3}$), 5.20(1H, dd, HA, JAB 10.7Hz, JAC 0.87Hz), 5.36(1H, d, HB, JAB 10.7Hz), 6.86(1H, d, Hc, JAC 0.87Hz), 7.47-7.93(3H, m, aromatic protons), 8.33(1H, complex d, C-8-H) ; $^{m}/e$ 262 [$M^{+\cdot}$] (39%).

(Found : C 55.0, H 3.9, N 10.8, S 12.5. $C_{12}H_{10}N_2O_3S$ requires C 54.9, H 3.8, N 10.7, S 12.2%).



1-Acetoxy-3,4-dihydro-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (231)

A mixture of the sulphoxide (228) (1.10 g) and acetic anhydride (10 ml) was heated at reflux until the reaction mixture was a very dark brown colour (ten minutes). The solid obtained following isolation by procedure (d) was recrystallised from ethyl acetate/light petroleum to give the pure acetoxy derivative (231) as a white powder, (530 mg, 41%) ; m.p. 142-143°C ; t.l.c. Rf(ethyl acetate/

light petroleum 1:1) 0.73 ; $\bar{\nu}$max (KBr) : 3065, 2980, 2950, 1750 (C=O ester), 1680 (C=O), 1605 (C=N), 1475, 1400, 1220 (C-O ester), 1010, 960, 770, 700 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.14(3H, s, $OCO\underline{CH_3}$), 3.05(2H, m, $>N-CH_2-\underline{CH_2}-S-$), 3.96(1H, m, $>N-\underline{CH_2}-CH_2-S-$), 5.52(1H, m, $>N-\underline{CH_2}-CH_2-S-$), 6.81(1H, s, $>\underline{CH}-O-CO-$), 7.43-7.89(3H, m, aromatic protons), 8.32(1H, complex d, C-8-H) ; $^m/e$ 276 [$M^{+\cdot}$] (11%).

(Found : C 56.8, H 4.4, N 10.3, S 12.0. $C_{13}H_{12}N_2O_3S$ requires C 56.5, H 4.3, N 10.1, S 11.6%).

1-Acetoxy-1H-4,5-dihydro-1,4-thiazepino(3,4-b)quinazolin-7(3H)-one (232)

The sulphoxide (229) (600 mg) and acetic anhydride (10 ml) were heated at reflux until complete dissolution occurred (one hour). Recrystallisation from ethanol of the solid obtained by procedure (d) gave the pure acetoxy derivative (232) as a white powder, (400 mg, 57%) ; m.p. 144-145°C ; t.l.c. Rf(ethyl acetate/triethylamine 9.1) 0.75 ; $\bar{\nu}$max (KBr) : 2920, 1740 (C=O ester), 1680 (C=O ring), 1605 (C=N), 1475, 1400, 1230 (C-O ester), 770 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.20(2H, m, $>N-CH_2-\underline{CH_2}-CH_2-S-$), 2.23(3H, s, $-OCO\underline{CH_3}$), 2.85 (2H, m, $>N-CH_2-CH_2-\underline{CH_2}-S-$), 4.35(1H, m, $>N-\underline{CH_2}-CH_2-CH_2-S-$), 4.95(1H, m, $>N-\underline{CH_2}-CH_2-CH_2-S-$), 6.91(1H, s, $>\underline{CH}-O-CO-$), 7.41-7.85(3H, m, aromatic protons), 8.27(1H, complex d, C-8-H) ; $^m/e$ 290 [$M^{+\cdot}$] (18%).

(Found : C 57.7, H 4.9, N 9.7, S 10.9. $C_{14}H_{14}N_2O_3S$ requires C 57.9, H 4.8, N 9.6, S 11.0%).

3-Acetoxy-1H-1-methylthiazolo[4,3-b]quinazolin-9(3H)-ones (269a) and (269b)

The sulphoxide (261) (2.15 g) and acetic anhydride (20 ml) were heated together at reflux for one hour. The acetic anhydride was removed in vacuo and the residue chromatographed on a column of silica gel (35 g). Elution with ethyl acetate/light petroleum (1:3) furnished a pale green syrup which rapidly crystallised. Recrystallisation from ethyl acetate/light petroleum gave the pure acetoxy derivative (269a) as a colourless crystalline solid, (970 mg, 38%) ; m.p. 171-172°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.36 ; $\bar{\nu}$max (KBr) : 2975, 2925, 1740 (C=O ester), 1680 (C=O ring), 1615 (C=N), 1470, 1380, 1220 (C-O ester), 1020, 960, 770 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.90 (3H, d, J 6Hz, >CH-$\underline{CH_3}$), 2.16(3H, s, -OCO$\underline{CH_3}$), 5.76(1H, q, J 6Hz, >$\underline{CH}$-CH_3), 6.76(1H, s, >$\underline{CH}$-OCO-), 7.10-7.80(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; ^{m}/e 276 [$M^{+\cdot}$] (18%).

(Found : C 56.3, H 4.6, N 10.0, S 11.7. $C_{13}H_{12}N_2O_3S$ requires C 56.5, H 4.35, N 10.15, S 11.6%).

Further elution with ethyl acetate/light petroleum (1:3) afforded a second isomeric acetoxy derivative (269b) as

colourless flakes following recrystallisation from ethyl acetate/light petroleum (900 mg, 35%) ; m.p. 131-132°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.33 ; $\bar{\nu}$max (KBr) : 2975, 2925, 1740 (C=O ester), 1680 (C=O ring), 1610 (C=N), 1470, 1370, 1220 (C-O ester), 1020, 950, 770, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.90(3H, d, J 6Hz, >CH-$\underline{CH_3}$), 2.16(3H, s, OCO$\underline{CH_3}$), 5.76(1H, q, J 6Hz, >$\underline{CH}$-CH_3), 6.76(1H, s, >$\underline{CH}$-OCO-), 7.10-7.80(3H, m, aromatic protons), 8.16(1H, complex d, C-8-H) ; ^{m}/e 276 [$M^{+\cdot}$] (17%).

(Found : C 56.6, H 4.4, N 10.1, S 11.3. $C_{13}H_{12}N_2O_3S$ requires C 56.5, H 4.35, N 10.15, S 11.6%).

3-Acetoxy-1H-1,1-dimethylthiazolo[4,3-b]quinazolin-9(3H)-one (270)

A mixture of the sulphoxide (262) (2.00 g) and acetic anhydride (25 ml) was heated at reflux until t.l.c. indicated no sulphoxide remained (fifteen minutes). The acetic anhydride was removed in vacuo and the residue chromatographed on a column of silica gel (20 g). Elution with ethyl acetate/light petroleum (1:9) furnished a green oil. Purification, by short path bulb to bulb distillation (Kugelrohr) at 200°C/1.5 mm Hg, gave the product (270) as a green glass, (1.30 g, 55%) ; m.p. 67.5-69°C ; t.l.c. Rf (ethyl acetate/light petroleum 1:1) 0.55 ; $\bar{\nu}$max (KBr) : 3080, 2995, 2945, 1755 (C=O ester), 1685 (C=O ring), 1600 (C=N), 1475, 1220 (C-O ester), 1020. 965, 780, 700 cm^{-1} ;

δ(60 MHz, $CDCl_3$) : 2.16(9H, s, $\chi\frac{CH_3}{CH_3}$, -OCO$\underline{CH_3}$), 6.76(1H, s, >$\underline{CH}$-OCO), 7.20-7.70(3H, m, aromatic protons), 8.18(1H, complex d, C-8-H) ; ^{m}/e 290 [$M^{+\cdot}$] (15%).

(Found : C 57.9, H 5.0, N 9.7, S 11.3. $C_{14}H_{14}N_2O_3S$ requires C 57.9, H 4.8, N 9.65, S 11.0%).

1-Acetoxy-1H-3,3-dimethylthiazolo[4,3-b]quinazolin-9(3H)-one (275)

A mixture of the sulphoxide (267) (800 mg) and acetic anhydride (15 ml) was heated at reflux until t.l.c. indicated no sulphoxide remained (twenty four hours). The reaction mixture was cooled, the acetic anhydride removed in vacuo and the residue chromatographed on a column of silica gel (10 g). Elution with ethyl acetate/light petroleum (1:4) gave a solid, which was recrystallised from ethanol to give pure (275) as a colourless crystalline solid, (650 mg, 69%) ; m.p. 134-136°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.35 ; $\bar{\nu}$max (KBr) : 2960, 2925, 1750 (C=O ester), 1690 (C=O ring), 1615 (C=N), 1465, 1220 (C-O), 770 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.78(3H, s, $\chi\frac{CH_3}{CH_3}$), 2.10(3H, s, -OCO$\underline{CH_3}$), 7.15-7.70(3H, m, aromatic protons), 7.71(1H, s, >$\underline{CH}$-OCO-), 8.16(1H, complex d, C-8-H) ; ^{m}/e 290 [$M^{+\cdot}$] (26%).

(Found : C 59.6, H 4.6, N 9.6, S 10.65. $C_{14}H_{14}N_2O_3S$ requires C 59.95, H 4.8, N 9.65, S 11.05%).

3,4-Dihydro-1-oxo-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (241)

The sulphoxide (239) (500 mg) and acetic anhydride (10 ml) were heated together at reflux for fifteen minutes. The acetic anhydride was removed *in vacuo* and the solid residue dissolved in ethyl acetate. After decolourisation and reconcentration *in vacuo*, the pure compound (241) was obtained by recrystallisation from ethyl acetate, (170 mg, 42%, yellow powder) ; m.p. 244-245°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.75 ; $\bar{\nu}$max (KBr) : 3000, 2930, 1670 (C=O anide), 1660 (C=O S-alkyl ester), 1600 (C=N), 1580, 1465, 1390, 950, 770 cm^{-1} ; δ(90 MHz, D_6DMSO) : 3.60 (2H, m, >N-CH_2-CH_2-S-), 4.62(2H, m, >N-CH_2-CH_2-S-), 7.56-7.99(3H, m, aromatic protons), 8.20(1H, complex d, C-7-H) ; $^m/_e$ 232 [$M^{+\cdot}$] (100%).

(Found : C 56.6, H 3.5, N 11.8, S 14.2. $C_{11}H_8N_2O_2S$ requires C 56.9, H 3.45, N 12.05, S 13.8%).

Attempted Pummerer Rearrangement of the Sulphoxide (263)

A mixture of the sulphoxide (263) (900 mg) and acetic anhydride (10 ml) was heated at reflux until t.l.c. indicated no (263) remained (thirty minutes). The acetic anhydride was removed in vacuo and the residue recrystallised from ethanol to give (273) as yellow prisms, (80 mg, 4.5%) ; m.p. 244-246°C dec. ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.55 ; $\bar{\nu}$max (KBr) : 2975, 2925,

1680 (C=O), 1600, 1590, 1465, 1320, 765, 695 cm^{-1} ; δ(90 MHz, $CDCl_3$) : 2.12(12H, m, methyl groups), 2.40-3.40(2H, m), 4.70(1H, m), 7.08(1H, m), 7.39-7.78(6H, m, aromatic protons), 8.26(2H, m, C-7-H) ; $^m/e$ 488 [$M^{+\cdot}$] (96%).

(Found : C 63.7, H 4.9, N 11.6, S 12.9. $C_{26}H_{24}N_4O_2S_2$ requires C 63.9, H 4.9, N 11.45, S 13.1%).

Deacetylation of Acetoxy Derivatives

1H-3-Hydroxythiazolo[4,3-b]quinazolin-9(3H)-one (233)

The acetoxy compound (230) (400 mg) was dissolved in sodium methoxide solution (prepared from sodium (100 mg) in methanol (30 ml)) and the resulting solution stirred at room temperature until t.l.c. indicated no acetoxy compound present (thirty minutes). The syrup obtained by procedure (f) was crystallised from ether and recrystallised from ethyl acetate/light petroleum to give the pure alkanol (233) as a white powder, (110 mg, 32%) ; m.p. 209-213°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.46 ; $\bar{\nu}$max (KBr) : 3500-3000 (O-H), 1690 (C=O), 1610 (C=N), 1470, 1035 (C-O), 780, 690 cm^{-1} ; δ(90 MHz, D_6DMSO) : 5.22(2H, s, >N-$\underline{CH_2}$-S-), 6.29(1H, broad d becoming a sharp s on deuteration, >$\underline{CH}$-OH), 7.35(1H, broad d, D_2O exchangeable, >CH-$\underline{OH}$), 7.49-7.99(3H, m, aromatic protons), 8.20(1H, complex d, C-8-H) ; $^m/e$ 220 [$M^{+\cdot}$] (26%).

(Found : C 54.9, H 3.8, N 12.85, S 14.6. $C_{10}H_8N_2O_2S$ requires C 54.5, H 3.6, N 12.7, S 14.5%).

3,4-Dihydro-1-hydroxy-1,4-thiazino[3,4-b]quinazolin-6(1H)-one (234)

To a solution of sodium methoxide (prepared from sodium (100 mg) in methanol (30 ml)) was added the acetoxy compound (231) (510 mg). The resulting mixture was stirred at room temperature for thirty minutes then treated according to procedure (f). The syrup so obtained was crystallised from ether and recrystallised from ethyl acetate/light petroleum to give (234) as a pale yellow powder, (110 mg, 25%) ; m.p. 161-163°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.52 ; $\bar{\nu}$max (KBr) : 3500-2700 (O-H), 1680 (C=O), 1605 (C=N), 1480, 1400, 1035 (C-O), 780, 695 cm^{-1} ; δ(90 MHz, D_6DMSO) : 3.20(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 3.40(1H, broad s, D_2O exchangeable, >CH-$\underline{OH}$), 4.15(1H, m, >N-CH_2-$\underline{CH_2}$-S-), 5.20(1H, m, >N-CH_2-$\underline{CH_2}$-S-), 5.82(1H, s, >$\underline{CH}$-OH), 7.54-7.89(3H, m, aromatic protons), 8.18(1H, complex d, C-7-H) ; ^{m}/e 234 [$M^{+\cdot}$] (12%).

(Found : C 56.4, H 4.4, N 12.1, S 13.4. $C_{11}H_{10}N_2O_2S$ requires C 56.4, H 4.3, N 11.9, S 13.7%).

1H-4,5-Dihydro-1-hydroxy-1,4-thiazepino[3,4-b]quinazolin-7(3H)-one (235)

The acetoxy compound (232) (750 mg) was added to a solution of sodium methoxide (prepared from sodium (100 mg) and methanol (30 ml)) and the resulting mixture stirred for thirty minutes at room temperature. Procedure (f) gave a yellow syrup, which rapidly crystallised on treatment with ether. Recrystallisation from ethyl acetate/light petroleum afforded the hydroxy derivative (235) as pale yellow prisms, (460 mg, 66%) ; m.p. 156-158°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.69 ; $\bar{\nu}$max (KBr) : 3330 (O-H), 2955, 2900, 1680 (C=O), 1680 (C=N), 1480, 1095 (c-O), 775, 700 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.00(2H, m, >N-CH_2-$\underline{CH_2}$-CH_2-), 3.00(2H, m, >N-CH_2-CH_2-$\underline{CH_2}$-), 4.60(2H, m, >N-$\underline{CH_2}$-CH_2-CH_2-), 5.95(1H, s, >$\underline{CH}$-OH), 7.25(1H, broad s, D_2O exchangeable, >CH-$\underline{OH}$), 7.48-7.88(3H, m, aromatic protons), 8.15(1H, complex d, C-8-H) ; ^{m}/e 248 [$M^{+\cdot}$] (3%).

(Found : C 57.65, H 4.9, N 11.4, S 12.9. $C_{12}H_{12}N_2O_2S$ requires C 58.1, H 4.8, N 11.3, S 12.9%).

1H-3-Hydroxy-1-methylthiazolo[4,3-b]quinazolin-9(3H)-one (271)

The acetoxy derivative (269a) (500 mg) and sodium methoxide solution (prepared from sodium (100 mg) and methanol (30 ml)) were stirred together at room temperature for thirty minutes.

Procedure (f) afforded a yellow solid which was recrystallised from ethyl acetate/light petroleum to give the pure hydroxy derivative (271) as pale yellow needles, (170 mg, 40%) ; m.p. 210-212°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.48 ; $\bar{\nu}$max (KBr) : 3500-3000 (O-H), 1650 (C=O), 1610 (C=N), 1465, 1020 (C-O), 775, 695 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.84(3H, d, J 6Hz, >CH-$\underline{CH_3}$), 5.70(1H, q, J 6Hz, >$\underline{CH}$-CH_3), 6.10(1H, s, >$\underline{CH}$-OH), 7.22(1H, broad s, D_2O exchangeable, >CH-$\underline{OH}$), 7.30-7.75(3H, m, aromatic protons), 8.05(1H, complex d, C-8-H) ; ^{m}/e 234 [$M^{+\cdot}$] (36%).

(Found : C 56.4, H 4.3, N 12.0, S 14.0. $C_{11}H_{10}N_2O_2S$ requires C 56.4, H 4.25, N 11.95, S 13.65%).

<u>1H-3-Hydroxy-1,1-dimethylthiazolo[4,3-b]quinazolin-9(3H)-one (272)</u>

To a solution of sodium methoxide (prepared from sodium (100 mg) and methanol (30 ml)) was added the acetoxy compound (270) (700 mg). The resulting mixture was stirred at room temperature for thirty minutes then treated according to procedure (f). The yellow solid obtained was recrystallised from ethyl acetate/light petroleum to give the alkanol (272) as pale yellow needles, (400 mg, 66%) ; m.p. 181-183°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.42 ; $\bar{\nu}$max (KBr) : 3500-2500 (O-H), 1695 (C=O), 1615 (C=N), 1480, 1370, 1035 (C-O), 780, 705 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.10(3H, s, C-1 methyl protons), 2.24(3H, s,

C-1 methyl protons), 2.24(3H, s, C-1 methyl protons), 6.28 (1H, s, >CH-OH), 7.10-7.70(4H, m, becoming 3H on deuteration, aromatic protons, >CH-OH), 8.18(1H, complex d, C-8-H) ; $^{m}/e$ 248 [$M^{+\cdot}$] (14%).

(Found : C 57.7, H 4.9, N 11.3, S 13.3. $C_{12}H_{12}N_2O_2S$ requires C 58.05, H 4.85, N 11.3, S 12.9%).

Halogenation

Attempted Bromination of (12)

A mixture of the quinazolinone (12) (1.00 g), N-bromosuccinimide (0.90 g, 1.2 mol. equiv.) and AIBN (10 mg) in carbon tetrachloride (30 ml) was heated at reflux for three hours. The solvent was removed in vacuo and the residue chromatographed on a column of silica gel (25 g). Decomposition of the material was observed and no products were isolated.

3,4-Dihydro-1-methoxy-1,4-thiazino[3,4-b]quinazolin-6(1H) -one (289)

A mixture of the quinazolinone (12) (3.00 g), N-bromosuccinimide (2.94 g, 1.2 mol. equiv.) and AIBN (50 mg) in carbon tetrachloride (100 ml) was heated at reflux for three hours. The solvent was removed in vacuo and the residue dissolved in methanol (50 ml). Sodium

methoxide (1.11 g, 1.5 mol. equiv.) was added, then the mixture heated at reflux for one hour. The methanol was evaporated in vacuo and the residue treated with dichloromethane (100 ml). The insoluble succinimide was removed by filtration, the mother liquors reconcentrated in vacuo and the residue chromatographed on a column of silica gel (20 g). Elution with ether/light petroleum (1:2) afforded a yellow solid which was recrystallised from ethyl acetate/light petroleum to give the pure methoxy derivative (289) as a colourless crystalline solid, (2.00 g, 58%) ; m.p. 105-106°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.62 ; $\bar{\nu}$max (KBr) : 3050, 2990, 2925, 2825, 1660 (C=O), 1600 (C=N), 1470, 1390, 1050 (C-O), 770, 740, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.04 (2H, m, >N-CH_2-CH_2-S-), 3.50(3H, s, O-CH_3), 3.90(1H, m, >N-CH_2-CH_2-S-), 5.36(1H, m, >N-CH_2-CH_2-S-), 5.36(1H, s, >CH-OCH_3), 7.25-7.70(3H, m, aromatic protons), 8.18(1H, complex d, C-7-H) ; $^m/_e$ 248 [$M^{+\cdot}$] (40%).

(Found : C 58.1, H 4.9, N 11.3, S 12.6. $C_{12}H_{12}N_2O_2S$ requires C 58.05, H 4.8, N 11.3, S 12.9%).

1-Carbomethoxymethylthio-3,4-dihydro-1,4-thiazino[3,4-b] quinazolin-6(1H)-one (290)

A mixture of the quinazolinone (12) (1.00 g), N-bromosuccinimide (1.10 g, 1.1 mol. equiv.) and AIBN (50 mg) in carbon tetrachloride (40 ml) was heated at

reflux for three hours. The solvent was removed *in vacuo* and the residue dissolved in THF (50 ml). A solution of methyl thioglycolate anion (prepared from methyl thioglycolate (1.1 mol equiv.) and sodium hydride (1.1 mol. equiv.) and sodium hydride (1.1 mol. equiv.) in THF (10 ml)) was added and the mixture warmed until t.l.c. indicated no bromo compound remained (15 minutes). The THF was removed *in vacuo* and the residue partitioned between ether (200 ml) and water (40 ml). The ethereal extracts were dried, decolourised, concentrated *in vacuo* and the residue chromatographed on a column of silica gel (15 g). Elution with ether/light petroleum (1:3) gave the pure ester (290) as colourless prisms, (480 mg, 32%) ; m.p. 123-124°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:1) 0.56 ; $\bar{\nu}$max (KBr) : 2930, 1730 (ester), 1680 (C=O ring), 1590, 1470, 1390, 1190 (C-O ester), 770, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.10(2H, m, >N-CH_2-CH_2-S-), 3.46(2H, s, -S-CH_2-CO_2-), 3.47(3H, s, -CO_2-CH_3), 4.26(1H, m, >N-CH_2-CH_2-S-), 5.16(1H, s, >CH-S-CH_2-CO_2-), 5.40(1H, m, >N-CH_2-CH_2-S-), 7.40-7.80(3H, m, aromatic protons), 8.20(1H, complex d, C-7-H) ; ^{m}/e 322 [$M^{+\cdot}$] (22%).

(Found : C 52.3, H 4.1, N 8.9, S 19.7. $C_{14}H_{14}N_2O_3S_2$ requires C 52.15, H 4.35, N 8.7, S 19.9%).

Reduction

3,4,11,11a-Tetrahydro-1,4-thiazino[3,4-b]quinazolin-6 (1H)-one (279)

Method 1

A solution of the thiazinoquinazolinone (12) (1.00 g) in glacial acetic acid (25 ml) was treated with sodium borohydride (0.87 g, 5 mol. equiv.). The mixture was stirred at 10°C for one hour then poured onto ice/water (250 ml). The resulting solution was extracted with dichloromethane (4 x 50 ml) and the combined extracts dried and concentrated in vacuo to give a yellow oil which was chromatographed on a column of silica gel (15 g). Elution with ethyl acetate/light petroleum (1:4) afforded the reduced quinazolinone (279) as colourless prisms following recrystallisation from ethyl acetate.light petroleum, (650 mg, 64%) ; m.p. 140-141°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.46 ; $\bar{\nu}$max (KBr) : 3290 (N-H), 3025, 2925, 1625 (C=O), 1515, 1460, 1415, 1330, 745, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.20-3.40(5H, m, >N-CH_2-CH_2-S-, -NH-CH-CH_2-S-), 4.75(1H, broad s, D_2O exchangeable, >N-H), 5.10(2H, m, >N-CH_2-CH_2-S-), 6.40-7.30 (3H, m, aromatic protons), 7.75(1H, complex d, C-7-H) ; $^m/_e$ 220 [$M^{+\cdot}$] (52%).

(Found : C 60.4, H 5.6, N 12.9, S 14.7. $C_{11}H_{12}N_2OS$ requires C 60.0, H 5.45, N 12.7, S 14.55%).

Method 2

A solution of the quinazolinone (12) (1.00 g) in absolute ethanol was treated with sodium borohydride (0.87 g, 5 mol. equiv.) and the mixture warmed for three hours. The solution was poured onto ice/water (200 ml), acidified with glacial acetic acid and concentrated *in vacuo*. Borate esters were removed by evaporation with methanol (3 x 50 ml). The residue was extracted with dichloromethane (3 x 50 ml). The dried combined extracts were concentrated *in vacuo* and the resulting syrup chromatographed on a column of silica gel (20 g). Elution with ethyl acetate/light petroleum (1:4) furnished (279) (800 mg, 79%) identical in all respects (m.p., ir, t.l.c., p.m.r.) to an authentic sample.

1-Carbethoxymethyl-3,4-dihydro-1,4-thiazino[3,4-b] quinazolin-6(1H)-one (280)

Phosphoryl chloride (15 ml) was cautiously added to a mixture of anthranilic acid (4.55 g) and 2-carbethoxymethyl -3-oxothiomorpholine (282) (7.61 g, 1.2 mol. equiv.) and the mixture heated on a steam bath for one hour. Procedure (a) afforded the crude product which was purified by chromatography on a column of silica gel (80 g). Elution with ether/light petroleum gave the pure ester (280) as a colourless crystalline solid (4.80 g, 47%) ; m.p. 129.5-131°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.38 ; $\bar{\nu}$max (KBr) : 2975, 2925, 1720 (C=O ester), 1675 (C=O ring),

1600 (C=N), 1470, 1370, 1230 (C-O), 770, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 1.28(3H, t, J 6Hz, $-CH_2-\underline{CH_3}$), 2.40-4.68(6H, m, $>\underline{CH}-\underline{CH_2}-CO_2-$, $>N-\underline{CH}-\underline{CH_2}-S-$), 4.15(2H, q, J 6Hz, $-\underline{CH_2}-CH_3$), 5.44(1H, m, $>N-\underline{CH}-CH_2-S-$), 7.20-7.65(3H, m, aromatic protons), 8.20(1H, complex d, C-7-H) ; $^m/e$ 304 $[M^{+\cdot}]$ (53%).

(Found : C 59.2, H 5.3, N 9.4, S 10.6. $C_{15}H_{16}N_2O_3S$ requires C 59.2, H 5.3, N 9.2, S 10.5%).

3,4,11,11a-Tetrahydro-1-(2-hydroxyethyl)-1,4-thiazino [3,4-b]quinazolin-6(1H)-one (283)

A mixture of ester (280) (3.80 mg) and sodium borohydride (2.36 g, 5 mol. equiv.) in absolute ethanol (100 ml) was heated at reflux for five hours. The reaction mixture was then poured onto ice/water (200 ml), acidified with glacial acetic acid and concentrated in vacuo. Borate esters were removed by evaporation with methanol (3 x 50 ml). The residue was extracted with dichloromethane (3 x 50 ml). The dried combined extracts were concentrated in vacuo to give a syrup which was chromatographed on a column of silica gel (40 g). Elution with ether/light petroleum furnished (283) as a pale yellow crystalline solid, (2.60 g, 78%) ; m.p. 171-173°C ; t.l.c. Rf(ethyl acetate/triethylamine 9:1) 0.25 ; $\bar{\nu}$max (KBr) : 3300(broad, OH, NH), 2900, 1630 (C=O ring), 1610, 1530, 1465, 1300, 1080 (C-O), 750, 690 cm^{-1} ; δ(90 MHz, D_6DMSO) : 1.69(2H, m,

-$\underline{CH_2}$-CH_2-OH), 2.10-3.30(4H, m, >N-$\underline{CH}$-$\underline{CH_2}$-S-, -NH-$\underline{CH}$-CH-S-), 3.60(2H, m, -CH_2-$\underline{CH_2}$-OH), 4.50(1H, t, D_2O exchangeable, -O-$\underline{H}$), 4.95(1H, m, >N-$\underline{CH}$-CH_2-S-), 5.50(1H, dd, becoming d on deuteration, -NH-$\underline{CH}$-CH-), 6.46-6.61(2H, m, aromatic protons), 7.07(1H, d, D_2O exchangeable, >N-$\underline{H}$), 7.20-7.30 (1H, m, aromatic proton), 7.52(1H, complex d, C-7-H) ; $^m/_e$ 264 [$M^{+\cdot}$] (30%).

(Found : C 59.3, H 6.05, N 10.6, S 12.0. $C_{13}H_{16}N_2O_2S$ requires C 59.1, H 6.05, N 10.6, S 12.1%).

Reaction of (283) with Para-toluenesulphonyl Chloride

Para-toluenesulphonyl chloride (800 mg, 1.1 mol. equiv.) was added to a solution of the alkanol (283) (1.00 g) in dry pyridine (30 ml). The reaction mixture was heated (steam bath) for five hours, during which time extensive darkening of the material was observed. The pyridine was removed in vacuo and the residue partitioned between sodium bicarbonate solution (30 ml) and dichloromethane (100 ml). The aqueous phase was extracted with further portions of dichloromethane (2 x 50 ml). The combined extracts were dried, concentrated in vacuo and the residue chromatographed on a column of silica gel (20 g). Elution with ether/light petroleum (1:1) afforded the cyclised compound (284) as fine colourless needles, (250 mg, 27%) ; m.p. 123-124°C ; t.l.c. Rf(ethyl acetate/light petroleum 1:3) 0.25 ; $\bar{\nu}$max (KBr) : 3050, 2975, 2900, 2850, 1650 (C=O),

1600, 1490, 1400, 1300, 755, 700 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.00-3.00(5H, m, -$\underline{CH_2}$-$\underline{CH_2}$-$\underline{CH}$<), 3.44(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.80(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 6.60-7.40(3H, m, aromatic protons), 7.80(1H, complex d, C-8-H) ; ^{m}/e 246 [$M^{+\cdot}$] (46%).

(Found : C 63.8, H 5.5, N 11.6, S 12.6. $C_{13}H_{14}N_2OS$ requires C 63.4, H 5.7, N 11.4, S 13.0%).

Oxidations with Peracetic Acid

3-(Quinazolin-4-oyl)methanesulphonic Acid (236)

A solution of the quinazolinone (11) (750 mg) and 30% hydrogen peroxide solution (2 ml) in glacial acetic acid (15 ml) was stirred at room temperature for fifteen hours. The resulting precipitate was removed by filtration and recrystallised from DMF to give the sulphonic acid (236) as a white powder, (440 mg, 44%) ; m.p. >350°C ; $\bar{\nu}$max (KBr) : 3500-2600 (O-H), 1715 (C=O), 1660 (C=N), 1380, 1260, 1215, 1180, 1040, 695 cm^{-1} ; δ(90 MHz, D_6DMSO) : 4.82(2H, s, >N-$\underline{CH_2}$-SO_3H), 7.52-7.86(3H, m, aromatic protons), 8.12(1H, complex d, C-5-H), 8.53(1H, s, -N=$\underline{C}$-$\underline{H}$) ; ^{m}/e 240 [$M^{+\cdot}$] (13%).

(Found : C 45.0, H 3.7, N 12.2, S 13.6. $C_9H_8N_2O_4S$ requires C 45.0, H 3.3, N 11.7, S 13.3%).

3-(Quinazolin-4-oyl)ethanesulphonic Acid (237)

A solution of the quinazolinone (12) (1.00 g) and 30% hydrogen peroxide solution (2 ml) in glacial acetic acid (15 ml) was stirred at room temperature for fifteen hours. The resulting precipitate was isolated by filtration and recrystallised from DMF to give the sulphonic acid (237) as a hydrated white powder, (600 mg, 47%) ; m.p. 344-345°C dec. ; $\bar{\nu}$max (KBr) : 3600-2500 (O-H), 1720 (C=O), 1660 (C=N), 1400, 1235, 1030, 770, 695 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.92 (2H, t, J 6.5Hz, >N-CH_2-$\underline{CH_2}$-SO_3H), 4.33(2H, t, J 6.5Hz, >N-$\underline{CH_2}$-CH_2-SO_3H), 7.49-8.07(3H, m, aromatic protons), 8.22 (1H, complex d, C-5-H), 9.01(1H, s, -N=C-$\underline{H}$), 11.40(1H, broad s, D_2O exchangeable, -$SO_3\underline{H}$) ; $^m/e$ 254 [$M^{+\cdot}$] (16%).

(Found : C 42.9, H 4.5, N 10.1, S 11.7. $C_{10}H_{10}N_2O_4S$. 1.3 H_2O requires C 43.2, H 4.6, N 10.1, S 11.6%).

1H-4,5-Dihydro-2,2-dioxo-1,4-thiazepino[3,4-b]quinazolin -7(3H)-one (238)

A solution of the thiazepino quinazolinone (13) (670 mg) and 30% hydrogen peroxide solution in glacial acetic acid (15 ml) was stirred at room temperature for fifteen hours. The reaction mixture was diluted with ethanol (30 ml) and warmed (steam bath) for five minutes to destroy any remaining peroxides. Evaporation of the solvents in vacuo yielded a solid, which was recrystallised from glacial

acetic acid to give the sulphone (238) as a white powder, (590 mg, 72%) ; m.p. 294-296°C ; $\bar{\nu}$max (KBr) : 2985, 2945, 1685 (C=O), 1595 (C=N), 1480, 1320, 1300, 1140, 1115, 780, 730, 695 cm^{-1} ; δ(90 MHz, D_6DMSO) : 2.15(2H, m, >N-CH_2-$\underline{CH_2}$-CH_2-SO_2-), 3.65(2H, m, >N-CH_2-CH_2-$\underline{CH_2}$-SO_2-), 4.56(2H, m, >N-$\underline{CH_2}$-CH_2-CH_2-SO_2-), 5.05(2H, s, =C-$\underline{CH_2}$-SO_2-), 7.47-7.96 (3H, m, aromatic protons), 8.15(1H, complex d, C-8-H) ; $^m/_e$ 264 [$M^{+\cdot}$] (100%).

(Found : C 54.1, H 4.6, N 10.45, S 11.7. $C_{12}H_{12}N_2O_3S$ requires C 54.5, H 4.5, N 10.6, S 12.1%).

Miscellaneous

2-(Methoxycarbonylmethylthiomethyl)quinazolin-4(3H)-one (286)

A solution of methyl thioglycolate anion (prepared by the addition of sodium methoxide (3.25 g, 1.1 mol. equiv.) to a solution of methyl thioglycolate (173) (5.85 g) in dry DMF (20 ml)) was added dropwise to a solution of 2-(bromomethyl)quinazolin-4(3H)-one (285) (12.00 g) in dry DMF (200 ml). The mixture was stirred at ambient temperature for forty eight hours then poured onto water (1,200 ml). The resulting precipitate was isolated by filtration and recrystallised from ethanol to give the pure ester (286) as colourless needles, (7.90 g, 60%) ; m.p. 150-151°C ; t.l.c. Rf(ethyl acetate/

triethylamine 9:1) 0.57 ; $\bar{\nu}$max (KBr) : 3050, 2900, 1735 (C=O ester), 1680 (C=O ring), 1610 (C=N), 1460, 1160 (C-O), 775 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.44(2H, s, -S-$\underline{CH_2}$-CO-), 3.64 (3H, s, $-CO_2-\underline{CH_3}$), 3.86(2H, s, =C-$\underline{CH_2}$-S-), 7.25-7.80(3H, m, aromatic protons), 8.20(1H, complex d, C-5-H), 11.76(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; $^m/e$ 264 [$M^{+\cdot}$] (33%).

(Found : C 54.7, H 4.4, N 10.3, S 11.9. $C_{12}H_{12}N_2O_3S$ requires C 54.55, H 4.55, N 10.6, S 12.1%).

2-(Methoxycarbonylethylthiomethyl)quinazolin-4(3H)-one (287)

A solution of methyl 3-mercaptopropionate anion (prepared by the addition of sodium methoxide (2.37 g, 1.1 mol. equiv.) to a solution of methyl 3-mercaptopropionate (288) (4.80 g) in dry DMF (20 ml)) was added dropwise to a solution of 2-(bromomethyl)quinazolin-4(3H)-one (285) (8.7 g) in dry DMF (100 ml). The reaction mixture was stirred at room temperature for forty eight hours then poured onto water (1,000 ml). The resulting precipitate was isolated by filtration and recrystallised from ethanol to yield the pure ester (287) as colourless needles, (6.70 g, 66%) ; m.p. 170-171°C ; Rf(ethyl acetate/ triethylamine 9:1) 0.48 ; $\bar{\nu}$max (KBr) : 3160, 3030, 2975, 1730 (C=O ester), 1670 (C=O ring), 1610 (C=N), 1470, 1360, 1165 (C-O), 780, 690 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 2.80(4H, m, -S-$\underline{CH_2}$-$\underline{CH_2}$-CO-), 3.60(3H, s, $-CO_2-\underline{CH_3}$), 3.64(2H, s,

=C-$\underline{CH_2}$-S-), 7.27-7.70(3H, m, aromatic protons), 8.12(1H, complex d, C-5-H), 12.10(1H, broad s, D_2O exchangeable, >N-$\underline{H}$) ; $^m/e$ 278 [$M^{+\cdot}$] (3%).

(Found : C 56.1, H 5.0, N 10.1, S 11.4. $C_{13}H_{14}N_2O_3S$ requires C 56.5, H 4.7, N 10.1, S 11.1%).

Attempted reduction of (286) and (287) with Sodium Borohydride in Acetic Acid

To a solution of (286) or (287) in glacial acetic acid (30 ml) was added sodium borohydride (1.25 g, 5 mol. equiv.). The mixture was stirred at room temperature for forty five minutes then poured onto ice/water (300 ml) and extracted with dichloromethane (3 x 50 ml). The dried, combined extracts were concentrated in vacuo and the residue chromatographed on a column of silica gel (20 g). The crude yellow oils so obtained decomposed on attempted short path bulb to bulb distillation.

Reaction of (12) with Thionyl Chloride

A solution of thionyl chloride (600 mg, 1.1 mol. equiv.) in dry dichloromethane (30 ml) was added dropwise to a solution of (12) (1.00 g) in refluxing dichloromethane (50 ml). During this addition a yellow precipitate formed. The reaction mixture was heated until homogeneous (three hours) then was washed carefully with water (50 ml). The

dried dichloromethane solution was concentrated *in vacuo* to yield a solid which was recrystallised from ethyl acetate to furnish the sulfine (288) as a yellow powder, (1.10 g, 90%) ; m.p. 184-185°C ; t.l.c. Rf(ethyl acetate/ light petroleum 1:1) 0.39 ; $\bar{\nu}$max (KBr) : 3050, 1680 (C=O), 1600 (C=N), 1460, 1390, 1330, 1085 (S=O), 1020, 770 cm^{-1} ; δ(60 MHz, $CDCl_3$) : 3.44(2H, m, >N-CH_2-$\underline{CH_2}$-S-), 4.40(2H, m, >N-$\underline{CH_2}$-CH_2-S-), 7.20-7.80(3H, m, aromatic protons), 8.00 (1H, complex d, C-7-H) ; $^m/_e$ 264 [$M^{+\cdot}$] (30%).

(Found : C 50.3, H 2.8, N 10.6, S 23.9. $C_{11}H_8N_2O_2S_2$ requires C 50.0, H 3.0, N 10.6, S 24.2%).

BIBLIOGRAPHY

1 Johne, S., Progress in the chemistry of organic natural products., (1984), 46.

2 Johne, S., Progress in drug research., (1982), 26, 259.

3 French Patent., (1970), 1 596 885.

4 British Patent., (1964), 972 977.

5 Hooper, D., Pharm.J., (1888), 18, 841.

6 Morris, R.C., Hanford, W.E. and Adams, R., J.Amer.Chem.Soc., (1935), 57, 951.

7 Spath, E. and Platzer, N., Chem.Ber., (1935), 68, 2221.

8 Landii Vittory, R. and Gatta, F., Gazz.Chim.Ital., (1969), 99, 59.

9 Mohrle, H. and Seidel, C.M., Chem.Ber., (1973), 106.

10 Chatterjee, A. and Ganguly, M., Phytochemistry., (1968), 7, 307.

11 Johne, S.V., Jing, B., Groger, D. and Radeglid, R., J.F.Prakt.Chem., (1977), 319(6), 919.

12 Jain, M.P., Atal, C.K., Bardhyopadhya, V.R. and Nagavi, B.G., Ind.J.Pharm,Sci., (1983), 45, 170.

13 Peterson, S. and Tietze, E., US Patent., (1962), 2 992 221.

14 Shakhidoyatov, Kh.M., Irisbaeva, A., Yun, L.M., Oripov, E. and Kadyrov, Ch.Sh., Khim.Getero.Soedin., (1976), 1286.

15 Oripov, E., Shakhidoyatov, Kh.M., Kadyrov, Ch.Sh. and Insbaeva, A., Khim.Prir.Soedin., (1976), 557.

16 Oripov, E., Shakhidoyatov, Kh.M., Kadyrov, Ch.Sh. and Abdallaev, N.D., Khim.Getero.Soedin., (1979), 684.

17 Taylor, E.C. and Shvo, Y., J.Org.Chem., (1968), 33, 1719.

18 Farmitalia Carlo Erba Spa. British Patent Appl., (1983), 2 103 207A.

19 Sharma, V.K. and Jain, M.P., Ind.J.Chem., (1983), 21B, 75.

20 Shakhidoyatov, Kh.M., Yamankulov, M.Ya. and Kadyrov, Ch.Sh., Khim.Prir.Soedin., (1977), 552.

21 Kametani, T., Yamanaka, T. and Nyu, K., J.Het.Chem., (1972), 9, 1281.

22 Shakhidoyatov, Kh.M., Oripov, E., Irisbaeva, A. and Kadyrov, Ch.Sh., Khim.Prir.Soedin., (1976), 825.

23 Dunn, A.D., Kinnear, K.I., Norrie, R., Ringan, N. and Martin, D., J.Het.Chem., (1987), 24, 175.

24 Shakhidoyatov, Kh.M. and Kadyrov, Ch.Sh., Khim.Prir.Soedin., (1977), 668.

25 Shakhidoyatov, Kh.M., Irisbaeva, A. and Kadyrov, Ch.Sh., Khim.Prir.Soedin., (1974), 681.

26 Shakhidoyatov, Kh.M., Irisbaeva, A., Yun, L.M., Oripov, E. and Kadyrov, Ch.Sh., Khim.Getero.Soedin., (1976), 1564.

27 Zharakeev, B.Kh., Telezhenetskaya, M.V., Khashimov, Kh.N. and Yunosov, S.Yu., Khim.Prir.Soedin., (1976), 679.

28 Deutsche Gold and Silberscheincleanstalt. Vormals Roessler, British Patent., 1 194 106.

29 Dunn, A.D. and Kinnear, K.I., J.Het.Chem., (1984), 21, 603.

30 Dunn, A.D. and Kinnear, K.I., J.Het.Chem., (1985), 22, 311.

31 Dunn, A.D., Kinnear, K.I., Barnes, J.C., Low, J.N. and Paton, J.D., Acta.Cryst., (1985), C41, 282.

32 Einhorn, A. and Liebrecht, A., Ber., (1887), 20, 1592.

33 Tschitschibabin, A.E., Ber., (1927), 60, 1607.

34 Hantzsch, A., Ber., (1899), 32, 3109.

35 Dunn, A.D., Kinnear, K.I. and Guy, E.L.M., J.Het.Chem., (1983), 20, 779.

36 Dunn, A.D. and Rudorf, W.D., Z.Chem., (1986), 26, 251.

37 Kendall, J.D. and Duffin, G.F., British Patent., (1950), 634 951.

38 Gupta, G.D. and Pujan, H.K., J.Ind.Chem.Soc., (1984), 61, 1050.

39 Khosla, M.C., Vig, O.P., Gupta, I.S. and Narang, K.S., Science and Culture (India)., (1952), 18, 43.

40 Griot, R.G., US Patent., (1966), 3 280 117.

41 Bhandari, K., Virmani, V., Padam, A.M., Jain, C. and Anand, N., Ind.J.Chem., (1979), 17B, 107.

42 Speckamp, W.N. and Hamersma, J.A.M., Tet.Lett., (1982), 23, 3811.

43 Daboun, H.A. and Abdel Aziz, M.A., Egypt.J.Chem., (1982), 26, 401.

44 Daboun, H.A. and Abdel Aziz, M.A., Arch.Pharm., (1983), 316, 394.

45 Adegoke, E.A., Alo, B.I., Familoni, O.B., J.Het.Chem., (1987), 24, 107.

46 Ishidate, M. and Hashimoto, Y., J.Pharm.Soc.Jpn., (1956), 76, 73.

47 Krickeldorf, H.R., Makromol.Chem., (1975), 176, 57.

48 Skinner, G.S. and James, J.C., J.Amer.Chem.Soc., (1961), 83, 1450.

49 Surrey, A.R. and Culter, R.A., J.Amer.Chem.Soc., (1954), 76, 578.

50 Bestian, H., Heyna, J., Bauer, A., Elhers, G., Hirsekorn, B., Jacobs, T. Noll, W., Weibezahn, W. and Romer, F., Ann., (1950), 566, 210.

51 Babichev, F.S. and Shokol, V.A., Ukrain.Khim.Zhur., (1956), 22, 215.

52 Lehr, H., Karlan, S. and Goldberg, M.W., J.Med.Chem., (1963), 6, 136.

53 Rabinovich, M.S., Shostakovskii, M.F., Levitov, M.M., Verkhovtseva, T.P., Kulikova, G.N., Preobrazhenskaya, E.V., and Kalinovskii, O.A., Zhur.Obshchei.Khim., (1961), 31, 1453.

54 Hill, R.K. and Cullison, D.A., J.Amer.Chem.Soc., (1973), 95, 2923.

55 Smythe, J.A., J.Chem.Soc., (1909), 95, 349.

56 Pummerer, R., Chem.Ber., (1909), 42, 2282.

57 Pummerer, R., Chem.Ber., (1910), 43, 1401.

58 Speckamp, W.N., private communication.

59 Russel, G.A., Janzen, E.G., Becker, H.D. and Smentowski, F.J., J.Amer.Chem.Soc., (1962), 84, 2652.

60 Russel, G.A. and Mikol, G.J. in "Mechanisms of Molecular Migrations", ed. Thyagarajam, B.S., Interscience, New York, (1968), 1, 157-207.

61 (a) Bordwell, F.G. and Pitt, B.M., J.Amer.Chem.Soc., (1955), 77, 572.

(b) Parham, W.E. and Bhausar, M.D., J.Org.Chem., (1963), 28, 2686.

(c) Johnson, C.R., Sharp, J.C. and Phillips, W.G., Tet.Lett., (1967), 5299.

(d) Parham, W.E. and Goren, S.H., J.Org.Chem., (1965), 30, 728.

62 Johnson, C.R. and Phillips, W.G., J.Amer.Chem.Soc., (1969), 91, 622.

63 Meervein, H., Zenner, K.E. and Gipps, R., Ann., (1965), 688, 67.

64 Tsuchihashi, G. and Ogura, K., Bull.Chem.Soc. Japan., (1971), 44, 1726.

65 Tin, K.C. and Durst, T., Tet.Lett., (1970), 4463.

66 Loeppky, R.L. and Chang, D.C.K., Tet.Lett., (1968), 3415.

67 Cinquini, M. and Colonna, S., J.Chem.Soc.Perkin 1, (1972), 1883.

68 Hojo, M. and Yoshida. Z., J.Amer.Chem.Soc., (1968), 90, 4496.

69 Bordwell, F.G. and Pitt, B.M., J.Amer.Chem.Soc., (1955), 77, 572.

70 Gilman, H. and Webb, F.J., J.Amer.Chem.Soc., (1940), 62, 987.

71 Wolfe, S. Rauk, A. and Csizmadia, I.G., J.Amer.Chem.Soc., (1967), 89, 5710.

72 Wolfe, S., Rauk, A. and Csizmadia, I.G., J.Amer.Chem.Soc., (1969), 91, 1567.

73 Wolfe, S., Rauk, A., Tel, L.M. and Csizmadia, I.G., Chem.Comm., (1970), 96.

74 Scholl, R., Ber., (1896), 29, 1824.

75 Dunn, A.D. and Kinnear, K.I., J.Het.Chem., (1986), 23, 53.

76 Sandstrom, J. and Wennerbeck, I., Acta.Chem.Scand., (1978), 32B, 421.

77 Dunn, A.D. and Norrie, R., J.Het.Chem., (1987), 24, 85.

78 Taylor, E.C. and Crovetti, A.J., J.Org.Chem., (1954), 19, 1633.

79 Fife, W.K., J.Org.Chem., (1983), 48, 1375.

80 Wieland, T. and Biener, H., Ber., (1963), 96, 966.

81 Dunn, A.D., unpublished observations.

82 Sharma, R.L., Dhar, K.L. and Atal, C.K., Ind.J.Chem., (1979), 17B, 444.

83 Chem. of carbon compounds, ed. Rodd, E.H., Vol 4a, 407, Elsevier Publishing Co., 1957, 1st Edition.

84 Kingsbury, C.A. and Cram, D.J., J.Amer.Chem.Soc., (1960), 82, 1810.

85 Chou, T.S. Burgtorf, J.R., Ellis, A.L., Lammert, S.R. and Kukolja, S.P., J.Amer.Chem.Soc., (1974), 96, 1609.

86 Meyers, A.I. and Greene, J.M., J.Org.Chem., (1966), 31, 556.

87 Taylor, E.C., McKillop, A. and Ross, R.E., J.Amer.Chem.Soc., (1965), 87, 1990.

88 Singh, B.D. and Chaudbury, D.N., J.Ind.Chem.Soc., (1970), 48(8), 759.

89 Bergman, J. Tilstam, U. and Tornroos, K.W., J.Chem.Soc., Perkin Trans.1, (1987), 519.

90 Brown, M.S. and Rapoport, H., J.Org.Chem., (1963), 28, 3261.

91 Truce, W.E., Birum, G.H. and McBee, E.T., J.Amer.Chem.Soc., (1952), 74, 3594.